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FAIGUE AVOIDANCE SCHEDULING TOOL (*FAST*) PHASE II SBIR FINAL REPORT, PART 1

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14. ABSTRACT
The purpose of the FAST™ Phase II effort has been to enhance the SBIR product. This was accomplished by adding features to the Fatigue Avoidance Scheduling Tool (FAST™), which contains a highly researched and recognized model of human sleep and cognitive performance and by conducting studies to acquire new data and to valid the model predictions. The Fatigue Avoidance Scheduling Tool (FAST™) allows a user to predict cognitive performance and effectiveness based on the timing and amount of sleep an individual or team receives prior to and during a mission. FAST™ provides the military planner the ability to optimize performance under conditions of limited sleep, thus minimizing the need for pharmacological aids while indicating work periods where additional fatigue countermeasure may be necessary. This report describes the rationale for adding features such as: shifting the circadian rhythm for shift work or transmeridian travel, automatically inserting sleep into a schedule when no data are available, predicting lapses of attention, an algorithm to predict the impact of stimulants on performance, a window showing levels fatigue factors affecting performance at any time within a schedule, and an algorithm to predict performance variability. The report also describes plans for future work that will develop new fatigue management tools. Part 2 of this report describes new interface designs for irregular schedules and shift work schedules as well as field study validation of the model predictions.

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PREFACE

All subjects were treated in compliance with AFI 40-402, and applicable FDA and HHS guidelines.

SUMMARY

Modern military operations are routinely conducted 24 hours a day in all but the worst of weather conditions. This operational tempo frequently deprives the soldier of the opportunity for appropriate rest. This SBIR effort has continued the development of a tool to assist commanders, medical doctors, planners and schedulers in scheduling activities and rest to optimize human performance and minimize errors and accidents.

Purpose of the Work

The purpose of the FAST™ Phase II effort has been to enhance a previously developed tool containing a highly researched and recognized model of human sleep and cognitive performance into an easily-used, computerized tool for military planners and schedulers. The Fatigue Avoidance Scheduling Tool (FAST™) allows a user to predict cognitive performance and effectiveness based on the timing and amount of sleep an individual or team receives prior to and during a mission. FAST™ provides the military planner the ability to optimize performance under conditions of limited sleep, thus minimizing the need for pharmacological aids while indicating work periods where additional fatigue countermeasure may be necessary.

Brief Description of the Work Carried Out

The Phase 2 effort was built on the Phase 1 developed FAST™ containing the Sleep, Activity, Fatigue, and Task Effectiveness (SAFTE) Model. This model predicts human cognitive performance and is recognized by the DoD as the most useful model of sleep and performance. The model is homeostatic in that it adjusts its predictions based on the recent sleep history of the projected population. In the model a circadian process influences both performance and sleep regulation. Sleep regulation is dependent on hours of sleep, hours of wakefulness, current sleep debt, the circadian process and fragmentation (awakenings during a period of sleep). Performance is dependent on the current balance of the sleep regulation process, the circadian process, and sleep inertia.

Building on the Phase I development effort, the contractor team, guided by government representatives, accomplished the following objectives for the Phase 2 effort and enhancement efforts.

1) Added parameters to the underlying model based on the existing research literature and data collected at the Brooks laboratory both previously and in the proposed effort,
2) Updated the software and GUI interface with Phase I lessons learned and from new information gained in the proposed effort,
3) Wrote and had AFSG approved a research protocol for a countermeasure study to acquire data for developing model parameters for stimulants,
4) Conducted a countermeasure study to acquire data for developing model parameters for a sleep aide,
5) Conducted a literature search to discover the sleep and rest habits of pilots during their discretionary (off-duty) time,

6) Demonstrated FAST™ to potential users and customers including other government agencies NASA, FAA and the commercial sector (airlines, railroad, trucking, etc.).

Work covering three additional objectives funded under the SBIR Enhancement Program is documented in Part 2 of this report.

Findings and Results

The SAFTE model exists independent of FAST™, its user interface. As such the work was separated into enhancements to the model and enhancements to the user interface, FAST™. It was hoped that data from studies ongoing at the time of the proposal would inform the SAFTE model regarding the performance of a special group of warfighters, pilots. Although these data were not available from pilots, other data from WRAIR were available to model the Psychomotor Vigilance Task (PVT). Many researchers view the PVT as the gold standard for assessing the effects of fatigue on human alertness and performance. The SAFTE model was enhanced to be predictive of the dependent measures of the PVT. In addition to this modeling effort, SAFTE was also modified to be predictive of the new findings resulting from the Sleep Dose Response (SDR) Study conducted at WRAIR (Balkin, Thorne, Sing, et al., 2000). This study restricted the sleep of the participants to either nine, seven, five or three hours per night for a week of nights. Upon completion of the restricted sleep treatment, participants received eight hours of recovery sleep for three nights and were released. Counter intuitively the participant's cognitive performance and PVT scores did not return to their baseline level measured prior to the restricted sleep treatment. This lead us to modify the SAFTE model such that it could predict the slow recovery effects uncovered in the SDR Study. The SAFTE model was enhanced to include an algorithm for shifting the circadian rhythm for transmeridian travel and shift work important for predicting aircrew performance during deployments and long airlift missions spanning one or more weeks. Although validating data were not available, Dr. Hursh developed a method for predicting the effects of stimulants on cognitive performance using data from Pigeau, et al. (1995). This enhancement to the model will be included when the algorithm is validated with additional single dose data and sleep effects data.

During the Phase 2 effort FAST™ was enhanced with several new features making the model more accessible and useful to users. The transmeridian phase shift algorithm was added to accommodate aircrews crossing multiple time zones and to predict the performance effects of shift workers. Also included on FAST™ displays is the illumination level on the earth continuously throughout a schedule. On the output side, FAST™ now prints a user-configurable, mission timeline showing events like takeoffs, waypoints, critical points, and landings along with the light conditions and performance effectiveness. A FAST™ display now allows a user to see the variability of performance predictions by turning on a user-selectable percentile marker in addition to the 50^{th} percentile. Other display outputs include a lapse index built on PVT data, a user-selectable criterion line for performance, and a summary table showing the amount of work time violating the criterion for fatigue. Also added is a dashboard showing five different fatigue factors at any point in a schedule.

In many cases a scheduler using FAST™ has no way of knowing how a person or crew might sleep for a given schedule. Unfortunately, studies of the sleep and rest habits in the pilot population were found to be absent from the research literature. A separate report was submitted under this contract detailing the methods, sources and approaches taken to discover this information. Fortunately, the Federal Railroad Administration was able to provide sleep and work schedules of railroad engineers that enabled the development of the Autosleep feature in FAST™. Autosleep is a method for automatically inserting sleep into the schedule that uses a few basic assumptions. Another feature added to FAST™ is a pre-schedule, three-day block that conditions the model for the sleep obtained prior to starting a schedule. This allows the model to adapt to larks and owls or other minor sleep time variations. Other enhancements to FAST™ include:

- Tabular data entries of sleep and work intervals.
- An event marker capability for either critical events or waypoints or both.
- Sleep quality with four levels.
- An optional blood alcohol concentration level axis.
- An optional continuous acrophase line spanning the entire schedule.
- An optional continuous sleep reservoir line spanning the entire schedule.
- An undo button.
- Selectable tables of the schedule's sleep, awake, and work intervals, and of event markers.
- A summary table containing the schedule attributes
- A selectable graph ordinate starting from 0 to 50%

FAST™ was also presented to selected AF operational units to provide information on operator acceptance and usability of the scheduling tool. In addition the USAFSAM training courses now provide fatigue management education and FAST™ training to their aerospace physiologists and flight surgeons. The AF FAST™ user population has grown to be quite large and is documented in this report with a list of AF beta testers and users. FAST™ has received user acceptance from the B-1 bomber schedulers at Whiteman AFB, the AFSG, Navy policy writers, and the FAA and NASA are using it to evaluate commercial airline schedules for excessive fatigue. NTI has actively attempted to interest other industries in FAST™ as well. A list of current and potential commercial customers is the report.

The human research proposed for this effort was somewhat disappointing. The sleep aids study, designed to show the benefits of sleep aids when daytime sleep was required, did not show any benefit over a quite, cool, dark facility. The research protocol for the proposed stimulant study was approved by the AFSG, but the AF laboratory could not fit the study into their schedule of priorities. Nevertheless, a stimulant algorithm was designed and tested with data from Pigeau, et al. (1995), but needs validation prior to inclusion in FAST™.

Future Directions for FAST™ Development and Spin-off Applications

There has been considerable activity in the FAST™ commercialization efforts toward the end of the Phase 2 contract. A summary of the key activities follow.

- NTI has created NOVA Scientific under its parent company NOVA Technology to market, sell and distribute FAST™ to business and commercial interests. NOVA is in the process of finalizing an agreement with Respironics, Inc. to jointly develop FAST™/MiniMitter products. The agreement is expected to be in place in November, the initial product effort has already been specified, and preparatory work on product development has begun.

- NOVA and Dr. Steve Hursh have made productive contact with companies in the aviation industry. Companies that we expect to start FAST™ evaluation include NetJets and Bombadier. Companies that are conducting FAST™ evaluations include American Airlines and Delta Airlines.

- We are preparing for an AF 6.3 effort by starting the design of a web version of FAST™. As soon as the funding is available (January, 2006 expected), we will make this a focal effort along with the redesigned user interface from the FAST™ Phase 2 to simplify interaction with the tool. Within the next 12 months, we will have web-based and stand-alone versions of FAST™ that are supported by a single code base.

- The FRA continues to be very supportive of FAST™. Dr. Hursh is in the process of preparing proposals for their next fiscal year that will provide additional FAST™ functionality that they have requested.

- NOVA will be preparing research proposals that will provide the validation and verification of extensions to the SAFTE model to include other performance factors such as Stress. This will provide the basis for expanding the FAST™ tool to become a more accurate and individual specific performance prediction tool.

- NOVA is preparing a support proposal for the Government that details the software version, software delivery, and support fees. While the FAST™ tool will be available at no charge for the Government, there will be a modest fee for support (technical support, web site maintenance, etc.).

Fatigue Avoidance Scheduling Tool
Phase II SBIR Final Report, Part 1

PHASE II FINAL REPORT

Over the last 10 years, fatigue and its management have been brought to the public's attention, by the National Sleep Foundation, by new laws regulating drivers of automobiles, and by organizations involved in long work periods and night operations. Military operations have long sought to "own the night" by developing technologies that exploit the cover of darkness. Aircraft guidance systems and smart munitions no longer require direct visual references to direct aircraft or munitions to their intended targets. The Air Force has extended the pilot's duty day by mid-air refueling methods that permit long duration flights that can take aircraft halfway around the world and back. Nevertheless, air operations still require the participation of human pilots, controllers, and ground support personnel to implement these lengthy missions. Physiologically the human brain cannot function for long periods of time without severe degradation. Further, it is not immune to variations in attention produced by the body's circadian rhythm normally occurring during day and night conditions. Fatigue is well known to degrade performance; and while countermeasures can temporarily extend the performance of crews under unusual circumstances, in the long run there is no substitute for adequate sleep to refresh mental capacity.

A great deal of research has been done to study the limits of human performance under sleep deprivation (Caldwell, 1997; Caldwell & Caldwell, 1998; Bonnet & Arand, 1994; Kreuger, 1989; Nicholson, 1987). Until FAST™ was created, there was no system that permitted the military planner to quantitatively consider the lessons of sleep and performance research when planning flight operations. The FAST™ Phase I SBIR effort developed a well-established and respected model of human sleep and performance into a useful computerized tool to assess potential schedules for the impact on fatigue. The idea was to give a scheduler or operator a decision aid that would allow fatigue to be avoided or minimized. This scheduling system would permit a planner to evaluate the relative benefits of various schedules that accomplish a mission. With this computerized system, optimal performance could be arranged at critical times and human degradations could be avoided, scheduled at times of minimal workload, or at times with the least operational impact. Alternatively, crews could be given rest or pharmaceutical countermeasures to enhance anticipated degraded performance.

In the Phase I report we described a variety of alternative approaches for managing fatigue in military operations (Caldwell, 1997; Lagarde & Batejat, 1995; Naitoh, Englund, & Ryman, 1982). These included monitoring performance to detect fatigue, using pharmacological stimulants to temporarily overcome fatigue, using sedatives to improve sleep at odd hours or under stress, taking short naps, and using a fatigue prediction model as part of a scheduling decision aid to guide the design of schedules to avoid, as much as possible, dangerous levels of fatigue. While each intervention may have an advantage under specific circumstances, a scheduling decision aid can help the planner avoid fatigue, and when mission demands would create unavoidable conditions of fatigue, the tool could suggest alternative strategies and interventions to correct the situation and maximize crew safety. Hence, the scheduling decision aid is the key to a comprehensive solution to the problem of fatigue.

Of the various alternatives for managing fatigue, monitoring and pharmacological stimulant/sedatives share the common disadvantage that they do not prevent fatigue, but merely react to the problem and attempt to correct for it during an operation. By the time it is indicated, performance degradation may have already occurred and mistakes may already have been made. Furthermore, the demands of an operation may conflict with the requirements for sleep or the use of a countermeasure and the fatigue may now be unavoidable. A more proactive approach projects alternative schedules for an operation against a model of the relationship between sleep and performance. Predicted levels of fatigue and performance provide information (data) for selecting a mission plan that optimizes performance. A model-based, scheduling approach has a number of important operational impacts:

- Operational planning automatically considers the latest empirical research on sleep and performance as summarized in the model
- Operational performance is preserved by scheduling required sleep when the operation permits
- Countermeasures are avoided or minimized to avoid the need to interrupt the mission or interfere with scheduled activities
- Naps may be deliberately scheduled to optimize performance with minimal disruption in crew operations
- Drug use is minimized to avoid abuse, side effects, or sleep "rebound"
- The risks of performance degradation are avoided by smart operational planning

The remainder of this report describes our attempt to enhance the SAFTE model and the FAST™ software making the model more accurate and the tool more useful to operational planners and schedulers. After listing the objectives of this project, the succeeding sections describe the work that was proposed for the project followed by the results of that work. The section entitled Work Performed describes the approach taken to meet the objectives, the problems encountered, and the new opportunities that presented themselves uncovered in the work. Task 1 of that section generally describes activities associated with development of the SAFTE model and Task 2 with their implementation in FAST™. Occasionally, much more of the effort is associated with SAFTE tasks compared with the implementation in FAST™. However, the opposite is also true where a feature is added to FAST™ to improve the user interface that has no effect on the SAFTE model. Therefore, complimentary sections under Tasks 1 and 2 will often be somewhat lopsided in the volume of text dedicated to the description of the work under each task.

The Results section also describes the outcomes separately for SAFTE and FAST™ and suffers from the same lopsidedness described above. The Results section also describes modifications to SAFTE and FAST™ that were not planned in the original Phase 2 or enhancement proposals. Occasionally, the Federal Railroad Administration funded this unplanned work. Alternatively, it may have been decided by the government/contractor SBIR team that the work was important and could be accomplished under the proposed budget. This additional work is documented in this report to give as complete a description of SAFTE and FAST™ as possible at this time.

Project Objectives

There were three main goals for the Phase II effort:

- Enhance the underlying sleep/performance model with new features based on experimental findings (e.g., fatigue countermeasures, transmeridian shifts)
- Modify the GUI interface to make it more easily used by military and other planners
- Demonstrate the potential for a commercial product

These goals were defined by six primary objectives:

1) To add parameters to the underlying model based on the existing research literature and data collected at the Brooks laboratory both previously and in the proposed effort,
2) To update the software and GUI interface with Phase I lessons learned and from new information gained in the proposed effort,
3) To conduct a countermeasure study to acquire data for developing model parameters for a stimulant(s),
4) To conduct a countermeasure study to acquire data for developing model parameters for sleep aides,
5) To conduct research to discover the sleep and rest habits of pilots during their discretionary (off-duty) time,
6) To demonstrate FAST™ to as many potential users and customers including other government agencies NASA, FAA and the commercial sector (airlines, railroad, trucking, etc.).

In the course of conducting the Phase II work three technical barriers emerged and three additional objectives were added and funded by an SBIR Phase 2 Enhancement.

7) To develop a ProActive Scheduling interface,
8) To develop a 24/7 Scheduling interface, and
9) To conduct Verification & Validation of the FAST™ model (SAFTE) with a report on the outcome.

Only the first six are documented in this report, Part 1. Objectives seven through nine are documented in Part 2.

Work Performed

For the FAST™ SBIR Phase II and enhancement efforts, the technical objectives were completed as described below.

Task 1: Extensions of the SAFTE Model

This task is devoted to upgrading the underlying model, SAFTE, for the FAST™ software tool. This task began at the start of the contract and continued throughout the effort tapering off as all the new variables to the underlying model were added. SAFTE is embodied in a form that is easy for the expert to make changes to its infrastructure, inputs and outputs. Extensive debugging commands and tools were used to carefully examine the consequences of various approaches to the modeling enterprise. Once equations were working properly and predictions were validated against data from the laboratory and literature, they were transitioned to the FAST™ software tool where they were programmed in Visual Basic and integrated into the GUI interface.

Each of the major model changes is described as a subtask to Task 1. Some subtasks were implemented immediately; others were delayed waiting on the outcome of the countermeasures studies of stimulants and sleep aids. The research team monitored the literature and several other active laboratories for new data that could be used to validate or extend the conditions under which the model makes cognitive performance or specific military task performance predictions.

Task Performance and Pilot Population Based Predictions Subtask (1.1)

During the Phase I SBIR effort, data from an on-ongoing, fatigue study at Brooks AFB using pilot participants was in the "data reduction" phase. Some of these data involved pilot participants flying a new flight simulator that had embedded performance measures. It was assumed that these data would reflect the performance of pilots flying in a fatigued state and might be used to model those effects for the SAFTE model. The concept was that a transformation of cognitive performance predictions, which was already modeled in SAFTE, could be used to predict the dependent flying performance measures of pilots. Potential AF users of FAST™ have requested that predictions be based on tests with pilot populations and that predictions be shown, as an option, in terms of changes in specific task measurements, such as "bombing error" or "reaction time to some task specific event." If this could be accomplished the effects of fatigue on several specific aircraft performance measures could be predicted by the model and plotted as a percentage of pilot baseline performance.

The results section of this task describes the problems associated with the hoped for data, the optimization of the SAFTE predictions for the Psychomotor Vigilance Task (PVT). The PVT (Dinges & Powell, 1985) is considered by some prominent researchers to be "the" most sensitive and reliable task for fatigue induced performance degradation. During the course of the Phase 2 effort, data became available from studies conducted by WRAIR concerning the performance effects of restricted sleep. The FAST™ team felt that the results of this study could both be used to provide prospective validation of model predictions and could inform the model regarding an unpredicted slow recover of performance. The model enhancements needed to predict these new findings are also described in the results section of this task.

Transmeridian Adjustment Subtask (1.2)

The scheduling tool must be able to evaluate schedules that transport the operator over time zones, with predictions of performance changes resulting from transmeridian desynchronization ("jet lag") and an algorithm to readjust to the new time zone ("re-entrainment"). The modifications to SAFTE to account for transmeridian relocation effects were developed from data in the literature.

The transmeridian algorithm was built on the basic premise that wake periods provide the entrainment stimuli that are the basis of phase adjustments to the temperature rhythm. The SAFTE algorithm was based on shift work and transmeridian travel research conducted by Dr. Tim Monk (Monk, 1991, Monk & Embry, 1981) and others (Klein & Wegman, 1980; Haus & Halberg, 1980). To compute times of light and dark for locations on the earth, algorithms

described by van Bochove (1982) were used. The results section for this task provides a brief description of the SAFTE algorithm followed by a more detailed description.

Countermeasures Effects on Performance Subtask (1.3)

A tool capable of predicting fatigue effects would be even more useful to military planners and flight surgeons if it could also predict the effects of fatigue countermeasures on performance. The operational planner needs a decision aid for when a countermeasure, such as a pharmacological stimulant, is needed, and a way to predict that the countermeasure will be adequate to assure successful performance at critical times in the mission.

It is always assumed that pharmacological interventions should be used sparingly, only when success of the mission or the safety of the crew is at stake. However, subjective judgments of fatigue are inadequate guides for arranging pharmacological countermeasures. A more complete fatigue model would provide an objective and reliable means for determining the optimal time for the administration of a countermeasure and would estimate the improvements in performance to be expected at critical mission times. Thus, the dose amount and schedule can be optimized for maximal benefit with minimal drug use. By projecting these effects in advance, the operational plan can incorporate the countermeasures and control risk with minimal amounts of drug.

In the proposal to this effort, studies were planned for and executed during the Phase 2 effort to acquire parameters for stimulant (Task 3) and sedative (Task 4) interventions and their effects on performance. Unfortunately, the data from these two studies did not support the development of the algorithms. However, another study in the literature was found that did provide proper data for countermeasure algorithm development.

The results section for this task describes the development of a stimulant effects algorithm based on Pigeau, Naitoh, Buguet, McCann, Baranski, Taylor, Thompson, and Mack (1995). They conducted a sleep deprivation study of both modafinil (300 mg) and dextroamphetamine (10 mg) given either prophylactically or after the onset of fatigue.

Sleep Timing Algorithm Subtask (1.4)

Based on user testing during Phase I, we found that many users will not know the sleep schedules of the crews, only their programmed time off-duty. However, the timing and duration of sleep is critical to performance predictions using the SAFTE Model. During Phase II, a separate model was developed to generate a typical sleep pattern based on a given work schedule. This required us to locate appropriate data to develop an algorithm to automatically schedule expected sleep periods during discretionary (off-duty) intervals that were consistent with normal practices in the subject population. Originally, this subtask was dependent on uncovering the sleep habits of pilots who were preparing for scheduled flights throughout the day and night (Task 5). Although the conclusion of this literature search revealed no published data on this topic and an AF study initiated out of the Aviation Safety Division of the AF Safety Center (AFSC/SEFL) to collect such data was never completed, alternate data were found that met some of the requirements for a sleep-timing algorithm. The parameters were developed

from Federal Railroad Administration data collected on short-haul railroad engineers working irregular schedules. The results section for this task describes the development of an auto sleep algorithm that was implemented in FAST™.

Task 2: Refinements to FAST™

This task is devoted to upgrading the FAST™ software tool. This task began soon after the start of the contract and continued throughout the effort to the end. Once equations were working properly in SAFTE and predictions were validated against data from the laboratory and literature, they were transitioned to the FAST™ software tool where they were programmed in Visual Basic and integrated into the GUI interface. Once the programmer was satisfied with the FAST™ implementation, the new software was shipped back to the modeler where test data were used to validate that the two implementations (SAFTE and FAST™) provided identical predictions. Prior to releasing each new version of the software, FAST™ was tested by all the members of the FAST™ team.

Mission Timeline Subtask (2.1)

User testing of Phase 1 FAST™ revealed a need to incorporate a method to permit tabular input of schedule information directly off the Air Tasking Order. The FAST™ team created a tabular data entry method in addition to the keystroke entry method in Phase 1 FAST™. An additional need emerging from discussions with pilots was for a mission timeline that contained information such as on-duty time, mission related events, such as take-off, refueling, target time, and landing. A tabular screen display and a printed mission timeline were created to answer this need. Based on previous work done for AF mission planners by AFRL/HEPF scientists, all this information plus time zone information and periods of en-route darkness were designed into the FAST™ displays and printouts. The concept of transmeridian travel was also accommodated in this subtask by adding a visual cue representing lighting conditions continuously throughout the mission. Since similar AFRL/HEPF timelines had already received user acceptance, there was no need to acquire additional user input prior to designing and programming the timeline table. Versions of the previously hand created timelines were used as a model. The results section for this task briefly describes the features of schedule timeline. A full description is contained in the Users Guide documentation for FAST™.

Alternative Populations and Performances Subtask (2.2)

After seeing and discussing the Phase 1 FAST™, users requested that the program provide options for tailoring the performance predictions to the expected performances of highly skilled pilots, rather that the average population. They also wanted options for the kind of performance metric that is predicted, in addition to the standard cognitive test battery currently used to guide predictions. It was anticipated that changes to SAFTE under Subtask 1.1 could be directly implemented in FAST™. However, this was not possible and will have to wait for new data.

SAFTE and FAST™ predict performance degradation from baseline for the average person under a given sleep and work schedule. Since there is a distribution around that average, it is important for a user to know the extent of that variability. The results section for this task describes the development of a method for showing the range of performance to be expected

around the prediction for the average person's performance under the schedule conditions. This is a component of FAST™, not of SAFTE.

Use and Effects of Fatigue Interventions Subtask (2.3)

User testing and discussions with the operational community indicated a strong interest in having the scheduling tool, FAST™, offer guidance to the user concerning the need for interventions, such as pharmacological aids or naps, and predictions of the enhancement in performance that could be expected from the intervention. After the SAFTE Model was extended to include these modulator effects (Objective 1), changes would be implemented in FAST™ to provide user help and predictions concerning interventions to counter fatigue. Although the stimulant and sleep aid effect predictions could not be implemented in SAFTE, and hence FAST™, additional countermeasures prompts were added to aid a user in making a decision to use a fatigue intervention. The results section for this subtask describes the addition of a user-selectable, limit that is displayed graphically warning of unacceptable performance degradation, of a dashboard of commonly accepted fatigue indicators, and of statistical data indicating the magnitude of the degraded performance exceeding the user-selected limit.

Sleep Schedule and Optimal Schedule Generation Subtask (2.4)

A design for automatically inserting sleep into a FAST™ schedule was created using the method implemented in SAFTE, Subtask 1.4. The method was developed on data provided by the Federal Railroad Administration (FRA) for short-haul railroad engineers working irregular schedules at all times of the day and night. The method of sleep prediction agrees well with data from the literature (Forie & Lantan, 1972). The FAST™ team of scientists and engineers also attempted to create a "recommended sleep schedule" to optimize performance in FAST™, but found that there were too many variables that could not be known and the approach was abandoned. However, the FAST™ team also enhanced FAST™ schedules to permit the user to enter "initialization values" to represent varying histories of sleep deprivation prior to the schedule in question. This will allow the tool to predict the effects on a population that starts the schedule in a state of partial sleep deprivation as well. The results section for this task briefly describes the implementation of the Autosleep method and of the addition of a pre-schedule, sleep-conditioning feature.

User Testing of FAST™ Subtask (2.5)

Because the FAST™ software was continually available during the Phase 2 and enhancement efforts and several users had ask for it to be available to them to use as it was being developed, there were ample opportunities to demonstrate new features to knowledgeable users when new versions were created. The results section for this task documents FAST™ usage with a list of beta testers and users.

Task 3: Studies of the Effects of Stimulants on Performance

Under extreme battle conditions, fatigue may be unavoidable. In those cases pharmaceutical agents can be used to maintain alertness. The purpose of this task was to conduct a study of the effects of modafinil on cognitive performance such that an algorithm could be created to capture

the time course of the effects. This unusual compound had been reported to restore alertness without the undesirable over-stimulation effects often reported with amphetamine like compounds. In the course of writing the research protocol to conduct the study, AFRL/HEPF scientists acquired additional funds to conduct an expanded study to examine dextroamphetamine and caffeine. A joint protocol was written that also included an assessment of the three stimulants on sleep. This protocol was reviewed and approved by the Brooks IRB and the AF Surgeon General's Office. Unfortunately, the study could not be implemented due to time constraints on the AFRL/HEPF scientists. This collaboration would have added tremendously to the science derived from the study because the three stimulants would be compared not only on performance, but also for their effects on sleep propensity. The benefit to the FAST™ product was that performance and sleep parameters for the three stimulants could be added to the model rather than just one stimulant funded by the SBIR. Air Force flight surgeons in operational units are anxious to have this information to combat fatigue on long duration and nighttime missions.

The above circumstance put the acquisition of stimulant data for developing SAFTE/FAST™ parameters in jeopardy. However, Drs. Wesensten and Balkin, WRAIR, had recently completed a study involving modafinil that might provide the data needed to develop stimulant effects parameters for SAFTE/FAST™ drug effects. In addition, Pigeau, Naitoh, Buguet, McCann, Baranski, Taylor, Thompson, and Mack (1995), who conducted a study of modafinil, dexamphetamine, and placebo during 64 hours of sustained mental work, also collected cognitive performance data from their participants. Based on their published data, Dr. Hursh has modeled the performance effects of d-Amphetamine (20 mg) and Modafinil (300 mg). Unfortunately, the Army scientists were not able to release the three stimulant study data to us for validating our parameter estimates.

The Pigeau, et al. data were used to develop specific parameters for the two fatigue countermeasures. The modeling of these data provides a first approximation to the stimulant algorithms for SAFTE/FAST™. The work on the research protocol is documented in the results section and the approved research protocol is included in Appendix 1.

Task 4: Studies of the Effects of Sleep Aids on Performance

Occasionally during a long duration mission, periods of low activity may occur that would be opportunities for naps to restore performance. Unfortunately, since many missions are conducted at nighttime, these periods may be during the day when sleep is difficult or they may be accompanied by heightened arousal in anticipation of a combat mission. During such times, sleep may be aided by a mild sedative if it certain that it would not interfere with cognitive ability after awakening from the drug. Zolpidem is a widely used sedative that may have minimal performance side effects. In Task 4 a study was conducted with participants undergoing experimentally induced fatigue and operating laboratory cognitive tasks used in piloting aircraft and in command and control operations. The purpose was to conduct a study of the effects of sleep aids on daytime sleep in an operational scenario evaluating cognitive performance such that an algorithm could be created to capture the time course of the effects. It was expected that the sleep aids would improve daytime sleep over placebo thus improving task performance during a subsequent night of testing. The findings have been submitted as an independent

technical report, but a short abstract of the study and conclusions are included in the results section.

Task 5: Studies of Sleep and Rest Habits in the Pilot Population and Comparison of Schedule Predictions

In order to develop a method to generate a typical sleep pattern based on a given work schedule, the literature was researched to discover how pilots use their off-duty time to obtain sleep in preparation for irregularly scheduled missions. If we could discover the sleep times and durations pilots selected to prepare for these missions, we believed it might be predictable and hence useful in FAST™. That is this information might allow us to develop an algorithm to automatically schedule expected sleep periods during off-duty intervals that would be consistent with normal practices in the subject population. The findings were submitted as an independent contract report, but a short abstract of the research process and conclusions are included in the results section.

Task 6: Demonstrate the FAST™ system to potential user populations both within and beyond the Air Force

Throughout the duration of the SBIR contract effort, potential customers in government agencies and commercial enterprise were identified as potential FAST™ users. We discussed with them their need for such a product and, whenever possible, demonstrated the then current version to them requesting feedback. The list of these potential customers is documented in the results section of this task.

Results Obtained

This section includes a brief description of the SAFTE model underlying FAST™ with references to publications describing it more thoroughly. The brief model description is followed by the results of the effort to enhance it during Phase II (Task 1). The next section describes FAST™ and its new features resulting from the Phase 2 work (Tasks 2). This section is followed by sections describing the results of the fatigue countermeasures studies (Tasks 3 & 4) and by a listing of potential users of FAST™ (Task 6).

The SAFTE Model

The Phase I technical report (Eddy and Hursh, 2001) and a publication Hursh, Redmond, Johnson, Thorne, Belenky, Balkin, Storm, Miller, & Eddy (2004), include a description of the historical background of the SAFTE model and detailed description of the model at the end of the Phase 1 effort. A brief review of the SAFTE model is included here to document the state of the model at the end of the Phase 1 effort so that the changes to the model completed during Phase 2 can be put in perspective.

The general architecture of the SAFTE model, as revised during Phase I, is shown in Figure 1. A circadian process influences both performance and sleep regulation. Sleep regulation is dependent on hours of sleep, hours of wakefulness, current sleep debt, the circadian process and

fragmentation (awakenings during a period of sleep). At any point in time performance is dependent on the balance of the sleep regulation process, the circadian process, and sleep inertia.

The model differs from others by having been optimized to predict changes in cognitive performance and incorporates features not included in any prior comprehensive model. It has a multi-oscillator circadian process, a circadian sleep propensity process, a sleep fragmentation process, and a circadian phase adjusting feature for time zone changes. The specific mathematical expressions that describe the model, the default values of all the variables, and the scientific references that are the basis of the models structures are described in Hursh, et al. (2004).

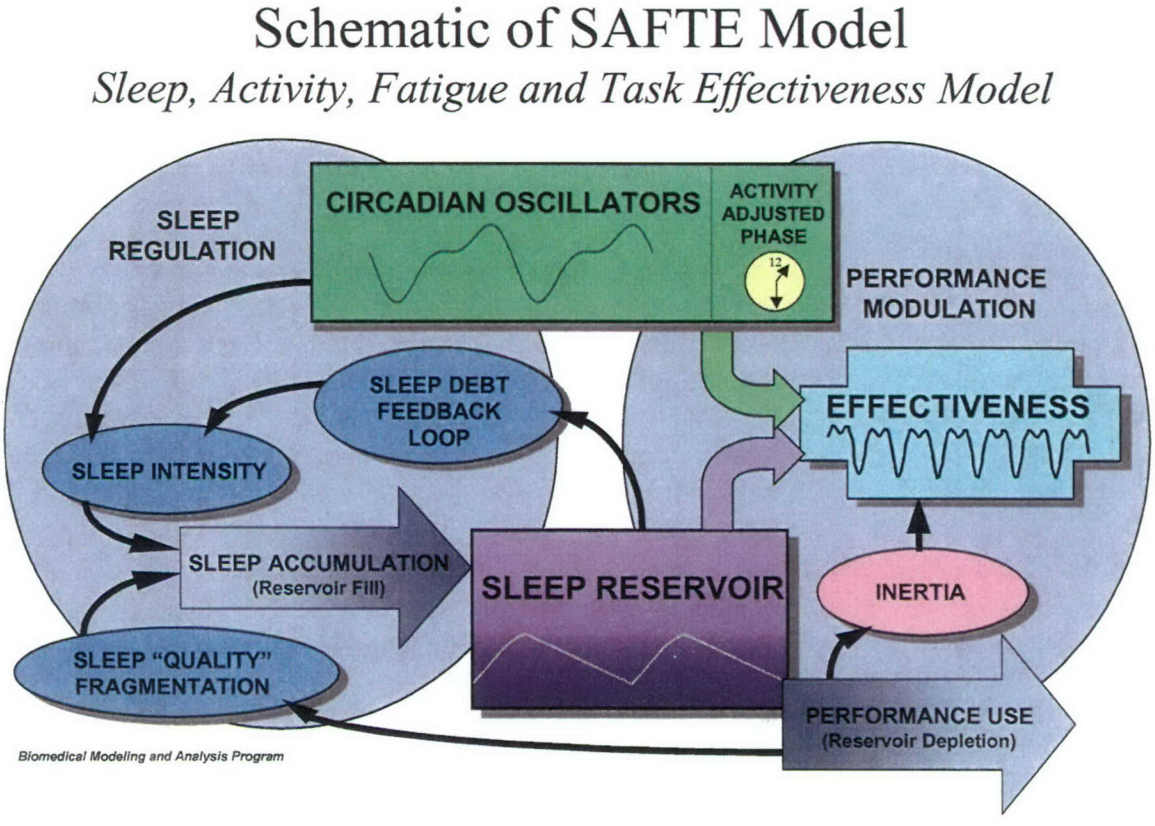

Figure 1. Block diagram of SAFTE model.

Circadian Oscillators. Performance while awake and the drive to sleep are both controlled, in part, by a circadian process. Studies of performance, alertness ratings, measures of the tendency to fall asleep, and body temperature indicate that the underlying circadian process is not a simple repeating sine wave. Performance and alertness reach a major peak in the early evening, about 2000 hours, and fall to a minimum at about 0400 hours. There is a secondary minimum in the early afternoon, about 1400 hours, and a secondary morning peak at about 1000 hours. Correlated with this pattern is a rising tendency to fall asleep that reaches a peak at about the same time performance and alertness reach their minima. The existence of both a major and a

minor peak in performance and two corresponding minima at other times suggests that at least two oscillators are involved in the circadian process.

The sleep and performance model incorporates a circadian process that is composed of the sum of two cosine waves, one with a period of 24 hours and one with a period of 12 hours. The two oscillators are out of phase, producing a predicted variation in arousal that closely parallels published patterns of body temperature. The circadian process within the model generates an arousal function that mirrors circadian changes in oral temperature. This arousal oscillator drives both variations in predicted cognitive effectiveness and sleep propensity. These two translations of the oscillator have identical frequency and phase components and differ only in amplitude and sign; a rise in arousal produces an increase in performance and a decrease in propensity to sleep. The circadian process is indicated in the large rectangle shown in the diagram of the SAFTE model, Figure 1.

Activity Adjusted Circadian Phase. When warfighters or others move to another time zone or alter work pattern so that sleep and work occur at different times of the day, the internal circadian oscillator that controls body temperature and alertness shifts to this new schedule. During the period of adjustment, people experience performance degradation, disrupted mood, and feelings of dysphoria known as circadian desynchronization or "jet lag". During Phase I SBIR, the SAFTE model was refined to mimic this process and automatically adjust the phase of the circadian rhythm to coincide with the activity pattern of the new schedule. This feature is critical for the accurate prediction of the effects of moving to a new time zone or changing to a new and regular work pattern (i.e. day shift to the night shift). The model detects the average time of the awake period and maintains a running average "awake time." The peak of the circadian rhythm has a reliable relationship to the timing of the period of wakefulness. When one moves to a new work schedule or a new time zone, the change in average awake time (relative to a reference time zone) is detected and a new "target phase" is computed. For example, when moving from the central US time zone to Germany, the awake time of a person advances six hours. Instead of waking at, say, 0600 Central Time, the subject awakens at 0000 Central Time, which is 0600 German time. This causes a shift of 6 hours in the "target phase" of the modeled person. However, the human physiological system does not adapt immediately to such a shift. In general, a phase advance (eastward time change) takes about 1.5 days per hour of shift. The model, therefore, adjusts to the new "target phase" gradually over the course of 9 days. During that time, the performance of the subject will show degradation due to the desynchronization of the internal circadian rhythm from the new rhythm of work and sleep. Likewise, westerly travel causes a phase delay in the circadian rhythm and research shows that phase delays take less time for adjustment, about one day per hour of shift, or six days for a six-hour time change.

The Sleep Reservoir and Homeostatic Sleep Regulation. The control of sleep and its influence on cognitive capacity is a homeostatic process. At the core of this process is a sleep reservoir, diagrammed as a rectangle at the center of the diagram in Figure 1. The model simulates the underlying processes that govern the capacity to perform. A fully rested person has a certain performance capacity indicated as the reservoir capacity, Rc. While awake, units of this reservoir are depleted each minute according to a linear performance use function, indicated by the arrow leaving the reservoir. While asleep, units of capacity are added to the reservoir each

minute to replenish the reservoir and the capacity to perform and be alert. The rate of accumulation for each minute of sleep is called sleep intensity and is driven by two factors: 1) the circadian variation in sleep propensity, and 2) the current sleep deficit, which is the reservoir capacity Rc, minus the current level of the reservoir at time t, Rt. This deficit is constantly changing as one sleeps and replenishes the reservoir, or is awake and depleting the reservoir. The oscillation in the reservoir level is called the sleep-wake cycle and reflects the current reservoir deficit. Note that sleep accumulation does not start immediately upon retiring to sleep. There is a brief delay of about 5 min required to achieve a restful sleep state. This factor accounts for the penalty during recuperation that is caused by sleep in an environment that leads to frequent interruptions. These components of the sleep accumulation function are indicated as ellipses in the diagram (Figure 1) to the left of the sleep reservoir feeding into the sleep accumulation function. The level of the reservoir at time t+1 is the level at time t, Rt, plus sleep accumulation (S) while asleep and minus performance use (P) while awake. The units of the reservoir are minutes of effective sleep. Since the model is a simulation, it can easily accommodate a complex pattern of sleep and waking. While asleep, the simulation adds to the reservoir; while awake the simulation depletes the reservoir. A schedule can oscillate between these states as often as once a minute and the simulation will keep account of the net effects on performance capacity as the balance in the reservoir, like the balance in a check book.

The outcome of the reservoir process in the SAFTE model during continuous sleep converges to an exponential accumulation function, and, as such, is similar to the "S" process (Sleep process) of the Folkard and Akerstedt (1991) three process model of sleep and performance. But at the molecular level the SAFTE model is based on minute-by-minute additions to the reservoir during sleep with the size of these increments proportional to the reservoir deficit (the feedback process). Integrated over time, this iterative process is described by an approximate exponential function. However, the model is not an exponential function; it is a moment-by-moment simulation of the effects of sleep on the reservoir balance. Hence, a momentary interruption in sleep (fragmentation) is simple to accommodate in the SAFTE model. The incremental process is interrupted for the duration of the awakening and the reservoir is depleted for that period of time by the performance function.

The feedback process explicitly included in the SAFTE model and implied by the exponential form of the Folkard and Akerstedt "S" process is critical in determining the effects of long schedules of less than optimal sleep. Such schedules deplete the reservoir and increase the intensity of sleep when sleep occurs. Eventually, the greater average intensity of sleep permits the person to adjust to such schedule and find a new equilibrium of sleep and stable performance, within limits. Performance will not be as effective as it might be with a full eight hours of sleep, but performance does not necessarily degrade indefinitely. It is much like a person adjusting to a restricted diet; the person looses weight and conserves energy so that a new equilibrium stable weight is reached under the limited input of calories.

Cognitive Effectiveness. Consistent with the approach proposed by Monk (1991) and Achermann and Borbely (1991), the model stipulates that cognitive effectiveness and alertness are primarily dependent on variations in the two processes just described: the endogenous circadian rhythm (reflected in oral temperature) and the current sleep reservoir balance resulting from the sleep-wake cycle, as diagrammed in Figure 2. A third factor, not shown, is the

temporary disturbance in performance that often occurs immediately following awakening, called sleep inertia (see Folkard and Akerstedt, 1991).

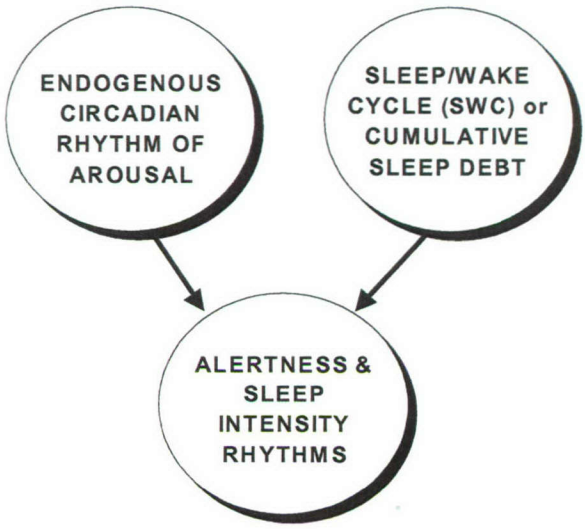

Figure 2. Major drivers of alertness and sleep regulation (after Monk, 1991).

Task 1 Results: Extensions of the SAFTE Model

This section describes changes made to the SAFTE model described above during the course of the Phase 2 effort. Although data were not available from pilots tested in a fatigue study, other data from WRAIR were available to model the Psychomotor Vigilance Task (PVT). In addition to this modeling effort, SAFTE was also modified to be predictive of the new findings resulting from the Sleep Dose Response (SDR) Study conducted at WRAIR (Balkin, Thorne, Sing, et al., 2000). This study restricted the sleep of the participants to either nine, seven, five or three hours per night for a week of nights. Upon completion of the restricted sleep treatment, participants received eight hours of recovery sleep for three nights and were released. Counter intuitively the participant's cognitive performance and PVT scores did not return to their baseline level measured prior to the restricted sleep treatment. This lead us to modify the SAFTE model such that it could predict the slow recovery effects uncovered in the SDR Study. This work on the model is documented in Subtask 1.1 below.

Subtask 1.1. Task Performance and Pilot Population Based Predictions

Pilot Performance. Dr. Kelly Neville's study of fatigue in pilots was not designed to test any particular hypotheses, but rather was designed to acquire data for a model of fatigue she was working on at the time. The study used a variety of computerized cognitive tests that had been shown sensitive to the effects of sleep depravation. In addition to five different cognitive test batteries in the study of fatigue in pilots, a new, desktop flight simulator using an F-16 aircraft model was used. As we stated in our objectives, our plan was to use the cognitive performance test data and the flight simulator data to construct a translation function that would predict the latter from the former. Unfortunately, the flying performance measures from the maiden flight of the simulator were flawed and did not accurately reflect the pilot's actual performance.

Therefore, we were unable to develop a transformation algorithm for predicting pilot flying performance under fatigue from cognitive performance test scores under fatigue.

Dr. French, a co-investigator on the study, did analyze the cognitive performance data from Dr. Neville's fatigue study and found that pilot performance on the cognitive tasks was similar to that of the subjects in the WRAIR experiments (Belenky, et al., 1996) used to create the algorithms relating sleep to performance in the SAFTE model. However, the pilot's data showed less vulnerability to fatigue (about 10% less) compared to the Army subjects. Since we only had one study at the time upon which to base a new algorithm for pilots, we did not include a unique prediction for the pilot subpopulation in SAFTE or FAST™, but have retained these data and analyses should additional data confirm these findings.

Regarding pilots as a unique sample from the population showing less vulnerability to fatigue, we have the following ideas. Should new data from pilots confirm this finding as reliable, the algorithm for a pilot population can be added to FAST™. However, considerable discussion will need to be devoted to how this is done. The FAST™ team will have to decide the criteria for adding predictions for new subpopulations in the future. Also, the impact of calling out one group as unique human beings with special qualities may be problematic for non-pilot predictions. It might be better to wait until research uncovers a variable that predicts individual differences to fatigue implying some causal relationship other than subpopulation membership before making such idiosyncratic predictions.

Unfortunately, neither Dr. Neville's study nor Dr. French's TR were never published; however, a publishable version does exist and has now been edited with Dr. French for publication as an AF technical report. The report required some corrections to the statistical analysis and is being submitted to HEPF for publication. Publication of the TR documents the cognitive performance data of pilots so that it can be used at a future time should other studies confirm the reduced vulnerability of pilots to fatigue. The study can be summarized as follows.

> *It had multiple goals, one of which was to evaluate the sensitivity of the Spaceflight-Cognitive Assessment Tool (S-CAT) to fatigue induced by sleep deprivation and circadian disruption. Since S-CAT had demonstrated sensitivity to organic neural dysfunction and it was expected to show fatigue sensitivity. Two groups of eight US military pilots (ages 30-40) were deprived of sleep for 46 hrs, over two circadian performance nadirs. In addition to S-CAT, four other cognitive performance tests were performed repeatedly during the sleep deprivation period. The S-CAT battery of tasks was performed once every six hours up to the 33rd hour while the participants were in the experimental situation. For all tests, the response time measures showed the greatest effects from fatigue. Two of the five S-CAT tests, a Matching to Sample and a Math test, exhibited significant fatigue-related decrements on response time. The Matching to Sample test and the Continuous Processing test showed effects on accuracy as measured by the percent correct responses. For Continuous Processing, 4 of 6 trials were affected, beginning after 23 hrs of wakefulness and lasting until 35 hours awake.*

Prediction of Specific Task Metrics and Modifications to SAFTE for Slow Recovery. The Psychomotor Vigilance Task (PVT) was developed by Dinges & Powell (1985) to substitute for a full up vigilance task like the Mackworth Clock Task (Mackworth, 1948). At the present time in the field of sustained operations research, many regard the PVT as the gold standard for assessing the impact of fatigue on performance. In addition many researchers have used performance on this task to compare the effects of various experimental interventions across

studies and as such have included this task in every study. Because of the respect afforded it, the FAST™ team decided to include it as the primary output for the SAFTE model and FAST™ software. Since its metrics correlate well with other cognitive tasks sensitive to sleep loss and circadian disruption, it was thought that optimizing SAFTE/FAST™ to predict its performance effects would be reasonably straightforward. At the same time, data from the Sleep Dose Response (SDR) Study became available and demonstrated that restricted sleep affected performance recovery in ways not seen with total sleep depravation. Dr. Hursh decided to modify the out of FAST™ to predict the PVT and to model the slow recovery effects of the SDR study. He used PVT speed expressed as a percent of baseline to develop the model parameters.

Once SAFTE was optimized for PVT, the predictions were compared with actual mean cognitive task performance data. On the ordinate of Figure 3, cognitive performance is based on the average of the cognitive tests (4-choice RT, 10-choice RT, PVT speed, and serial add/subtract) administered in the WRAIR Sleep Dose Response (SDR) study and expressed as a percentage of baseline throughput. These data are plotted against SAFTE predictions where SAFTE has been optimized for PVT speed. The plot shows the relationship to be very good, $R^2 = 0.967$, with the PVT showing greater sensitivity than the combined cognitive tests. That is, the PVT shows more degradation than the mean for other cognitive tests across all the restricted sleep conditions.

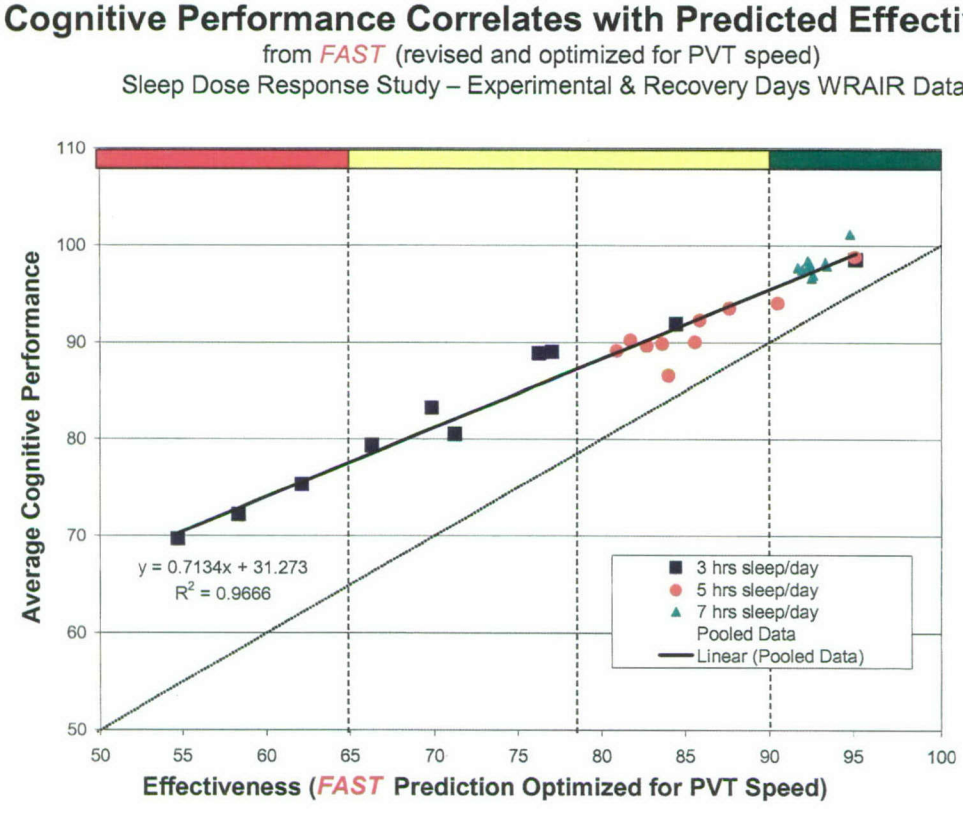

Figure 3. This linear regression shows that average cognitive performance from the SDR study is easily predicted by SAFTE when optimized for PVT speed. Since the best fitting line is above the diagonal, PVT is more sensitive to fatigue than the average cognitive test.

An examination of the residuals for the average cognitive metric is shown in Figure 4. Once the baseline PVT speed is linearized with the proper regression coefficients it is seen that there are no systematic deviations that would obfuscate or distort the linear relationship.

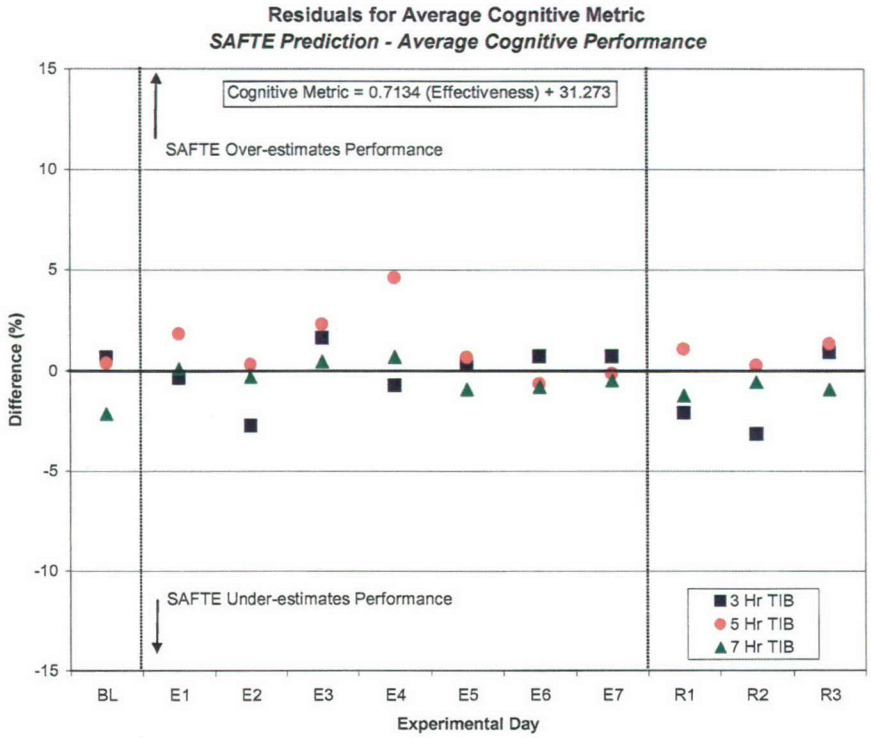

Figure 4. An examination of the residuals predicting average cognitive performance from SAFTE predicted PVT speed. The different colored points represent the different restricted sleep conditions from the SDR Study.

Thereafter, each of the sleep-restricted groups was separately examined using predictions from the PVT optimized model for PVT speed. What is obvious from Figure 5 is that deviations from baseline PVT speed with little or no fatigue are not well predicted by the model. However, when sleep is restricted to five or seven hours per night, the model makes very accurate predictions of PVT speed degradation. As expected, an analysis of the residuals for PVT Speed, Figure 6, shows the distortion for the seven-hour sleep group to be located at the end of the restricted sleep week and during the recovery period.

Extending these predictions to PVT lapses, defined as response times greater than 500 msec., we must first convert SAFTE predictions from a rate measure (throughput) to time per item by taking the reciprocal of effectiveness. With these transformations the number of lapses as a percentage of baseline (~1) was plotted against the reciprocal effectiveness prediction of SAFTE. Figure 7 shows that effectiveness nicely predicts lapse increases from baseline in the three- and five-hour restricted sleep groups, $R^2 = 0.80$. An analysis of the residuals from these predictions is shown in Figure 8.

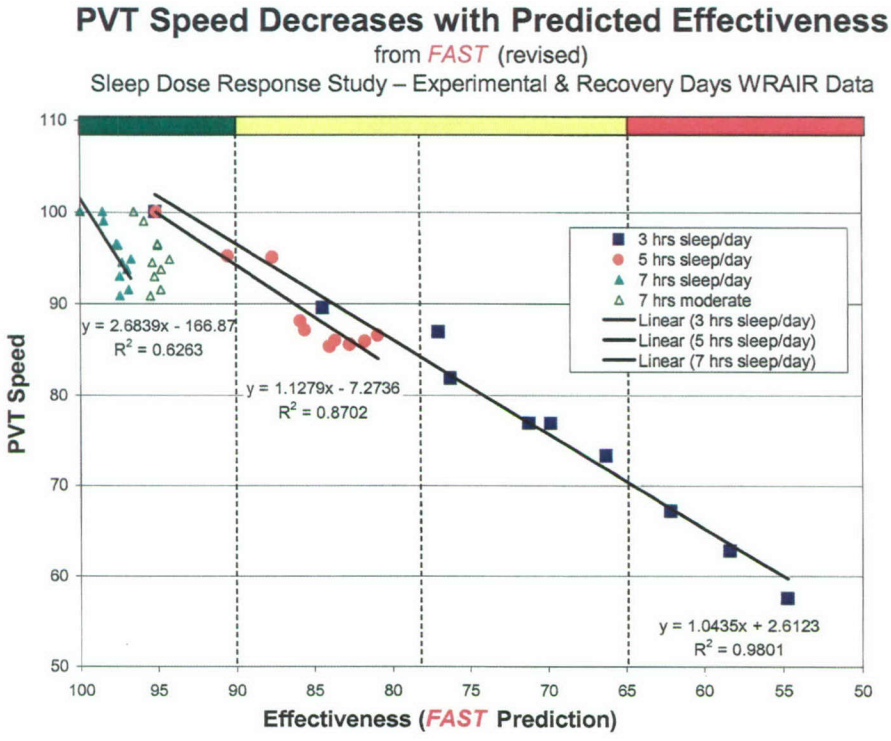

Figure 5. This graph shows SAFTE/FAST™ predictions of effectiveness correlate well with PVT speed from each of the sleep-restricted groups, excepting the 7-hour group.

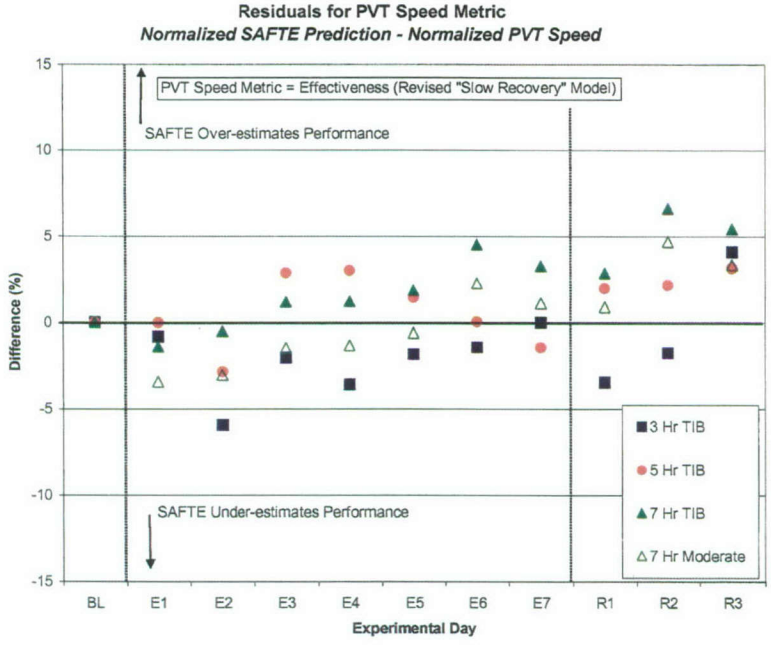

Figure 6. This graph shows the PVT residuals from the model predictions.

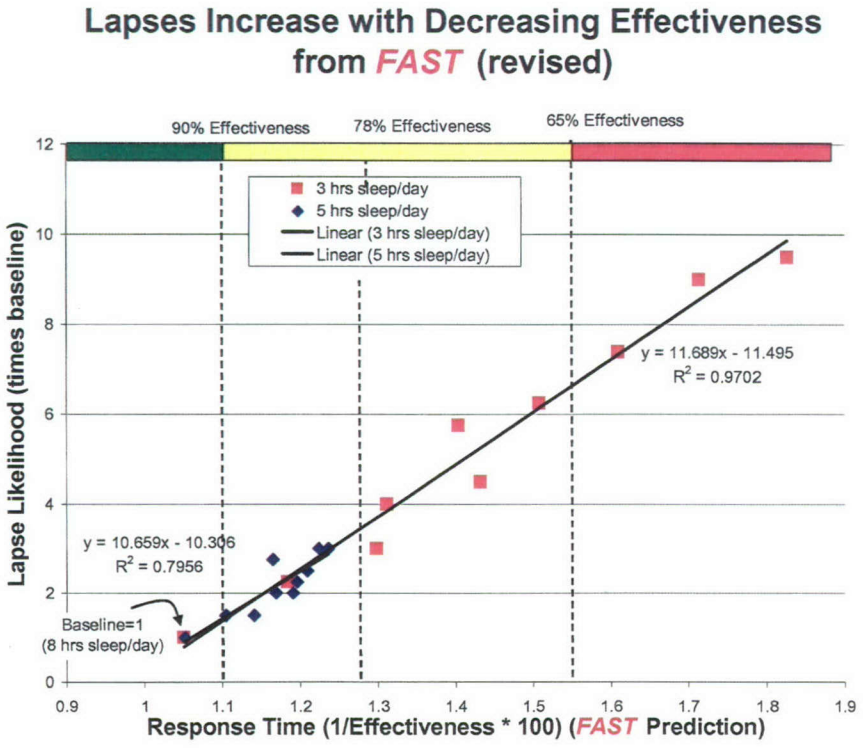

Figure 7. This scatter plot shows PVT lapses well predicted by SAFTE reciprocal effectiveness.

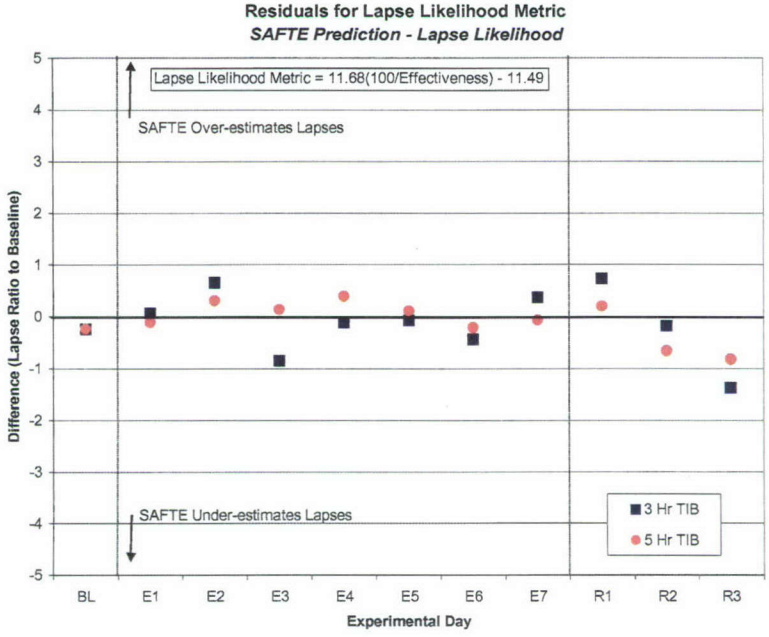

Figure 8. This plot shows the residuals for PVT lapse predictions from SAFTE reciprocal effectiveness for the three and five hour time in bed (TIB) groups.

As stated earlier, the results of the SDR Study provided an opportunity to both conduct a prospective validation of the SAFTE Model against a range of sleep conditions between total sleep deprivation and normal amounts of sleep and also to extend the model to account for slow recovery of performance. The SDR study restricted the sleep of the participants to either nine, seven, five or three hours per night for seven days and then provided eight hours of recovery sleep for three nights. Counter intuitively the participant's cognitive performance and PVT scores did not return to their baseline level measured prior to the restricted sleep treatment. Our approach to these data was to normalize the data relative the average performance across all cognitive tasks for the group provided 9 hours of sleep. This group was important because it accounted for the clear learning effect that occurred with some of the tasks. The model does a reasonably good job of predicting the average performance during the course of the 7 days of sleep restriction but does not predict the slow recovery during the 3 days of recovery sleep.

The relatively permanent effect of chronic sleep restriction suggests that some aspect of sleep homeostasis undergoes a gradual change that is slow to recover. Within the context of the SAFTE Model, a simple gradual down-regulation of the sleep reservoir capacity (Rc) during chronic restriction can account for this change. A single equation modulates Rc during sleep:

Equation 1. $$Rc_{(t)} = Rc_{(t-1)} + t \cdot [k_1 \cdot [1 - (SD_{(t-1)}/k_2)] + k_3 \cdot (2880 - Rc_{(t-1)})],$$

where $SD_{(t-1)}$, is the sleep debt component of sleep intensity at time t - 1, $[f(Rc_{(t-1)} - R_{(t-1)})]$. As before, SP is the sleep propensity, the circadian component of sleep intensity. Parameter f is the amplitude of feedback in the original model and $R_{(t)}$ is the current reservoir balance. The exact value of f is adjusted to a slightly higher value (0.00312) when implementing Equation 1 to ensure that a person getting 8 hours of sleep per day is in balance. Based on the SDR study, the limit of Sleep Inertia (SI) is reduced to 3.4 units per minute. In addition, Equation 1 is constrained so that when Rc is restored it may not exceed the full capacity of 2880, as represented in the original version of the model. No changes to Rc occur during awake periods. The specific mathematical expressions that describe the model, the default values of all the variables, and the scientific references that are the basis of the models structures are described in Hursh, et al. (2004). Good fits to data are achieved with constants about equal to those in Table 1.

Equation 1 functions as follows: the first expression within brackets becomes negative when Sleep Dept (SD) exceeds k_2 and down-regulates Rc according to the rate constant k_1; when SD is less than k_2, then the second expression within brackets tends to gradually restore Rc according to the rate constant k_3. Jointly, this expression tends to down-regulate Rc when sleep intensity is high ($> k_2$) and to restore Rc when sleep intensity is low ($< k_2$). During a normal 8-hour period of sleep, Rc is down-regulated slightly and is restored by the end of the night. During prolonged periods of restricted sleep, Rc is down-regulated more than it is restored so that a gradual shift in the reservoir "set point" occurs. If we think of SD as a measure of "sleepiness," then this process tends to reduce sleepiness by reducing the difference between the current reservoir level and the reservoir capacity or "set point." During periods of restricted sleep, performance tends to be more severely degraded (compared with the original model) because the reservoir reaches equilibrium at a reduced set point. During recovery sleep, performance recovers more slowly

(compared with the original model) because both the level of the reservoir and the reservoir capacity must be restored.

The heavy lines in Figure 9 are the predictions of the modified SAFTE Model optimized for average cognitive throughput and using the parameters listed above for Equation 1. This version of SAFTE makes identical predictions for total sleep deprivation, so the results of fits to total sleep depravation study results such as Angus & Heslegrave (1985) are unchanged. The R^2 (2) for this fit to the mean cognitive performance observed in the SDR study is 0.94.

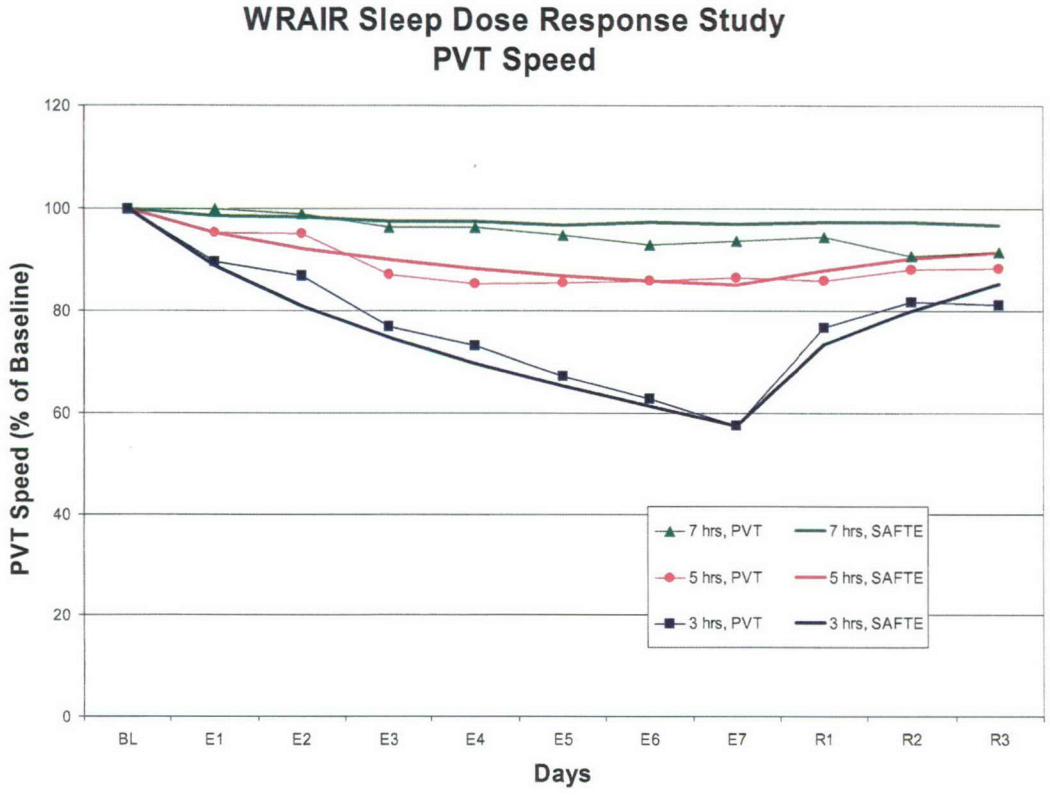

Figure 9. This graph displays the fit of the modified SAFTE model to the average PVT speed from the SDR Study. The lines in the figure indicate the predictions of the revised SAFTE Model using actual sleep durations (R^2 = 0.94). Results are shown for the baseline, seven experimental days (E1-E7), and three recovery days (R1-R3).

To summarize the changes to the SAFTE model for PVT performance and slow recovery, Table 1 lists the parameters. Table 1 also includes the parameters for the mean of cognitive tasks from the original model.

Table 1. SAFTE Parameters for Predicting Average Cognitive Performance or PVT Speed.

Parameter	Optimized for Average Cognitive Task	Optimized for PVT Speed
24-hr rhythm acrophase	18	18
12-hr rhythm phase offset	4 hours	3 hours
Relative amplitude of 12-hr rhythm	0.5	0.5
Sleep propensity mesor	0	0
Sleep propensity amplitude	0.5 sleep units	0.55 sleep units
Maximum sleep accumulation / minute	3.4 sleep units/minute	3.4 sleep units/min.
Performance rhythm amplitude (fixed percent)	10%	7%
Performance rhythm Amplitude (variable percent)		5%
Reservoir capacity	2880 sleep units	2880 sleep units
Feedback amplitude	0.002587	0.0031200
Sleep inertia time constant	0.07	0.04
Maximum inertia following awakening (percent)	10%	5%
Performance use rate	0.5 units per minute	0.5 units per minute
Relative acrophase	3	3
Sleep environment		
– Excellent	1	1
– Moderate	0.83	0.83
– Poor	.5	.5
Slow recovery model parameters		
– K1, down regulation time constant		0.22
– K2, reference level for sleep inertia regulation		0.5
– K3, recovery time constant		0.0015

Subtask 1.2. Transmeridian Adjustment

Changing from one time zone to another frequently presents problems for pilots deploying around the world. In addition, changing from a day shift to a night shift, or visa versa, can create temporary performance degradation until the circadian rhythm adapts to the new work/rest time periods. To our knowledge, no one has proposed a specific methodology, or theory, for predicting a change in cognitive performance that changes as people adjust their circadian rhythm. Our general rationale for changing the phase of the circadian rhythm is described next and was tested in SAFTE and then implemented in FAST™.

In SAFTE, the model estimates the timing of light exposure from the timing of the wake period on the assumption that people normally like to be in lighted areas. This works for most but not all operational settings. The algorithm considers only awakenings longer than 1 hr. This is

important for odd schedules and for actigraph data that is full of short awakenings during sleep. The model keys off the center of the wake period because this method treats awakenings at different times differently. To give the system stability, a weighted mean of the last three awakenings is used, with the most recent awakening most heavily weighted. Location information is used to calculate sunrise and sunset. However, that information is not used to directly set a goal phase. Instead, the method described above is used for the goal phase and then the light information is used to modulate the rate of adjustment to that goal. If sleep is mostly occurring during solar darkness, then it is assumed that the shift is transmeridian and adjusts 1 hr per 1 day for West travel and 1 hr per 1.5 days for East travel. If sleep is occurring during solar light, then the model assumes that the person is doing shift work and increases the duration of adjustment accordingly. Compared to transmeridian travel, the model assumes shift work takes three times longer to adjust the circadian rhythm to a new sleep time.

A basic premise of the current model is that awake periods provide a strong entrainment stimulus that serves as the basis of phase adjustments to the circadian rhythm. Hence, the time of the awake period is the primary factor determining the phase (beginning) of the circadian rhythm. At the end of each awake period the model computes a new RUNNING AVERAGE AWAKE HOUR, which is the average of that awake period averaged with the average awake hour of the prior two awake periods. Though the current model uses the awake period, this is not to imply that there are not other entrainment stimuli for adjusting the phase of the circadian rhythm such as bright light, activity, etc. Also, brief awakenings during the night lasting only a few minutes (less than 20 minutes) are disregarded.

Based on the running average awake hour, the model computes a new GOAL Acrophase as the running average awake hour PLUS 3 hours (a variable). For an awake time from 08 to 24 (average of 16), that gives an acrophase of 19, which is the current default.

The model adjusts the current acrophase each minute by comparing the goal to the prior current acrophase. If the difference is greater than 1 hr (+/-1), it starts adjusting the acrophase by 1/1440 of an hour for each minute of delay or 1/2160 of an hour for each minute of advance (variables). It adds or subtracts, depending on whether the difference is + or -. If the difference is less than an hour, it adjusts by that difference times 1/1440 each minute. It checks to see if the difference is greater than 12 hours, in which case it is shorter to go in the opposite direction. In that case, the current acrophase is adjusted by + or – 24, and the direction of change is reversed.

The result is a model that adjusts about one hour a day per hour of phase delay and one hour per 1.5 days for each hour of phase advance. It adjusts smoothly and continuously so that it will also deal with rotating shifts, in which case the goal acrophase shifts back and fourth and the adjusting acrophase keeps trying to find the goal at the prescribed rate, but never gets there unless the schedule stabilizes. Other factors, such as bright light (Weaver, 1985) or diet, could be incorporated into the model in the future as factors that change the rate of adjustment of the physiological rhythm to the predominant schedule represented by the goal acrophase.

Definitions.

1. AVERAGE AWAKE HOUR: The average awake hour of any awake period is based on the average clock time of the awake period – so a period from 0800 hrs to midnight would have an average clock time of 1600 hrs (the middle of the period).

2. The RUNNING AVERAGE AWAKE HOUR is the average of the average awake hours for the last three awake periods. The three periods are weighted so that the period just ended has equal weight to the previous two periods and the previous period twice the weight of the period prior to it, i.e. (1x + 0.67y + 0.33z) / 2.

3. GOAL ACROPHASE: This is the AVERAGE AWAKE HOUR plus a constant displacement, which is currently set at +3 hours. This gives a 'standard' acrophase of 1900 hrs for a 16-hour awake period from 0800 hrs to midnight.

4. ADJUSTING ACROPHASE: Since the biological phase cannot shift in one big jump to the GOAL ACROPHASE, this calculation adjusts it at a rate of one hour per day for phase delays or 2/3 hour per day for phase advance until it is within 1 hour of the goal, and then gradually approaches it from that point to zero deviation.

Calculations.
Running Average awake hour
Given:
CA = Cumulative minutes awake at end of awake period.
TAE = Time of awake period end
AH_n = Average awake hour for awake period *n*.
AV = Running average awake minutes

At the end of each awake period, calculate new AV, where $n = 0$ is just ended awake period, $n = -1$ is previous awake period, and $n = -2$ is awake period prior to that.

Equation 2a, AH_n , Average Awake Hour for awake period *n*:

AH_n = If (TAE - (CA / 60) < 0), then (TAE + 24 + (TAE + 24 -(CA / 60))) / 2),
Else (TAE + (TAE -(CA / 60))) / 2)).

Equation 2b, RA, Running Average Awake Hour:

$AV = 0.33 * AH_{-2} + 0.67 * AH_{-1} + AH_0) / 2.$

Explanation:
(TAE - (CA / 60)) is the time of the start of the awake period in hours.

(TAE + (TAE - (CA / 60))) / 2 calculates the average awake hour as the simple average of the beginning time and ending time.

AV is calculated as the weighted average of the last three awake periods, such that the just ended period has weight equal to the prior two periods, and the prior period has a weight twice that of the period prior to it.

Goal acrophase

Given: RA = A parameter that sets the RELATIVE ACROPHASE based on the average awake hour. For example an RA=2 gives an acrophase of 18 by adding it to the average awake hour of 16 for a awake period from 0800 to 2400. This is a parameter.

GA = Goal Acrophase

Then: at the end of each awake period, calculate a new goal acrophase:

Equation 3: $GA = AV + RA$

Explanation:
The acrophase of the arousal/temperature rhythm is set relative to the average awake hour. That is the essence of using the awake time as the entrainment stimulus for the phase shifting model. As average awake hour shifts with a new schedule or time zone, then the goal acrophase adjusts also. The actual phase of the temperature rhythm does not adjust immediately to this new goal acrophase, but gradually moves toward it according to the adjustment algorithm discussed next.

Adjusting acrophase - phase correction algorithm

Given: CP = Current Acrophase
PC_a = Amount of Phase Change in minutes for each hour of advance, default value is 2160 minutes per hour of advance (eastward flight direction).
PC_d = Amount of Phase Change in minutes for each hour of delay, default value is 1440 minutes per hour of delay (westward flight direction).

Then: at each minute of schedule, adjust the current acrophase according to the following algorithm:

Equation 4:
If GA = CP, then no change.

If CP < GA, : Phase Delay
Then, If GA-CP>1,
If GA-CP>12, then New CP = Old CP + 24 – $1/PC_a$
Else, New CP = Old CP + $1/ PC_d$
Else, New CP = Old CP + (GA-CP)*$1/ PC_d$

If CP >= GA, :Phase Advance
Then, If CP-GA>1,
If CP-GA>12, then New CP = Old CP – 24 + $1/ PC_d$
Else, New CP = Old CP – $1/ PC_a$
Else, New CP = Old CP + (GA-CP)*$1/ PC_a$

Explanation:
The initial IF statements test for which is greater, Goal Acrophase or Current Acrophase. The outcome determines which way to move the current acrophase, i.e. phase delay or advance.

The next level of IF statements determines if the difference is greater than one hour, the basic unit of change. If it is greater than one, then we move the acrophase by +/-1/PC hours; if it is less than one, the we change acrophase by the difference times 1/PC. This gives us an average rate of change of about 1/PC and then approaches the Goal value gradually.

The next level of IF statements determines if the difference is greater than 12 hours, in which case we subtract or add 24 as appropriate and move in the opposite direction. This determines the shortest distance and adjusts the direction of change accordingly.

Note that the method of change when the difference is less than 1 hour is the same expression, regardless of which is greater, GA or CP. This is because the (GA-CP) term will have the appropriate sign to move in the correct direction.

Model Predictions

Time Zone Changes

The model makes the following strong predictions for the effects of a 6-hr transmeridian flight in either east or westbound direction. These could be tested to validate or calibrate the model:

1. Westbound flights of 6-hrs produce little disruption during regular working hours (local time) because work coincides with a time when the endogenous rhythm is generally approaching its peak. Full adjustment in the late evening takes 6-7 days.
2. Eastbound flights of 6-hrs produce more disruption during regular working hours (local time) because work now coincides with a time when the endogenous rhythm is approaching its low point. Full adjustment in the morning takes 9-10 days.
3. After a time zone change, the closer one awakes to the new schedule the better.
4. Naps may enhance performance by making up for lost sleep, but if taken at odd hours will either have no effect on the readjustment or will delay it.
5. Performance decrements (compared to preflight) could still occur with westbound flights during the evening hours (2000 to 2400 hrs), new local time, for the first 4-5 days post flight.
6. Performance enhancements (compared to preflight) might actually occur on eastbound flights if performance is measured in the early morning hours (0200 to 0600 hrs), local time, on the first 1-3 days post flight.

Shift work Adjustments

The model makes the following predictions for shift work that could be tested:

1. When shifting to nights, regardless of sleeping schedule, large disruptions in performance will occur toward the end of the shift in the early morning.
2. When shifting to the night shift from the day shift, sleeping in the morning (0800-1600) will hasten the adjustment to the schedule, but performance will be impaired in the early morning hours (0200-0600), even after the adjustment.

3. Alternatively, when working nights, adjusting sleep pattern so that it has the same relation to the time of work as the day work schedule, such as sleeping from 1200-2000, will prolong adjustment, but will prevent the early morning impairment of performance.
4. Finally, if sleep periods on the night shift are taken in two, 4-hour blocks in the morning (0800-1200) and evening (1700-2100), an accumulated sleep debt will occur that produces a general disruption in performance that persists even after the phase change is complete.

Transitions to day work following night work (if phase was fully adjusted on night work) will produce a general disruption during the day work that could last for a week. However, disruptions are never as severe as they are during the early morning hours on the night shift.

Phase Adjustment to Light

The above algorithm is modified in the following way to account for the effects of light on phase adjustment. The logic of this modification is that it uses light information to determine if the individual has undergone a transmeridian shift or a phase shift in the same location, as for shift work. We will use the standard rates of circadian phase change for the transmeridian shifts and slower rates for shift work based on the shift work literature. Note that we are not attempting to precisely model the laboratory studies of light effects on the grounds that in the real working world the rates of adjustment to shift work are the combined effects of light on physiology AND the effects of activity as well as social and environmental cues. Hence, we use the reported rates of change in body temperature in shift-workers as a summary of the effects of all those inhibiting factors.

Percent Sleep Light During Sleep-Seasonally Corrected

The rate of phase change for an advance or a delay is adjusted for the percent of the sleep period that coincides with daylight. This percentage is corrected for the amount of darkness available based on latitude and season of the year. For low percentages of daylight during sleep, rates of adjustment are as indicated above for adjustments to transmeridian relocation. For larger percentages of daylight during sleep, the rate of adjustment is progressively reduced to reflect the slower rates of adjustment indicative of shift work (see Monk, T., Knauth, P., Folkard, S., et al., 1978). The calculation is as follows:

Percent Sleep Light = (Hrs Light Asleep / Total Hrs Asleep) - (Minimum Hrs Light / Total Hrs Asleep)

Minimum Hrs Light = Total Hrs Asleep - Total Hrs Dark in 24 hrs, if < Total Hrs Asleep, else = 0

Figure 10 shows that across 27 cases, a cut off of 16.7% daylight during sleep will segregate most transmeridian shifts from most shifts in place (shift work). The exceptions are 3 hr advances in-place because it is often still dark 3 hrs prior to normal bedtime.

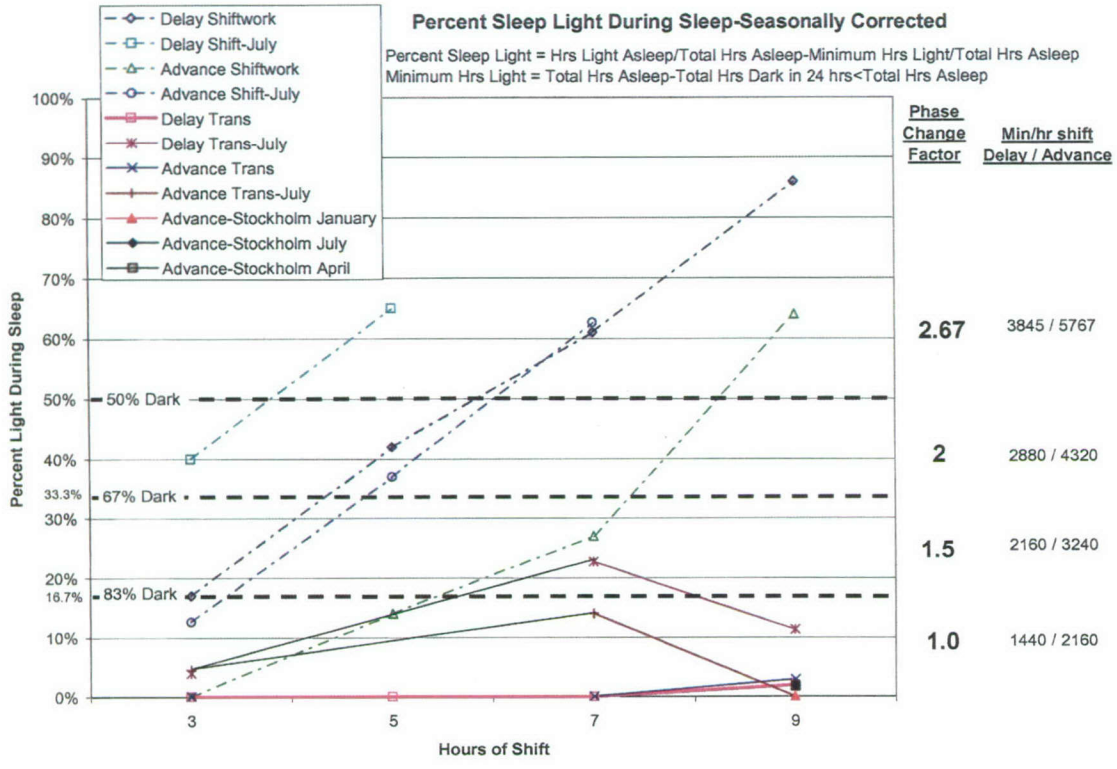

Figure 10. Calculation of percent daylight during sleep (y-axis) and comparison to an array of phase shifts (x-axis), with and without transmeridian relocation. The legend provides additional detail.

Using the suggestion of Dr. Miller, AFRL/HEPM, four percentage ranges were defined for determining rate of shift, as shown in the Figure 10 and Table 2. This algorithm has been implemented in FAST™ with the existing data available. It required no change to the user interface. A test platform was created to work through the series of specific test cases shown above and others with variable sleep times and durations.

Table 2. The Phase Change Factors.

Percent Sleep Light	Phase Change Factor	Resulting Rates of change (minute per hour of phase change)	
		Delay (PC_d)	Advance (PC_a)
0% – 16.7%	1.0	1440	2160
16.7% – 33.3%	1.5	2160	3240
33.3% - 50.0%	2.0	2880	4320
> 50.0%	2.67	3845	5767

Transmeridian Relocation Effects ("Jet Lag")

The transmeridian relocation feature was added to FAST™ to predict the adaptation of performance to changes in time zones that might accompany transmeridian flights or that might occur if aircrew are shifted to a regular schedule of night time work. Figure 11 displays the adjustment of performance to two flights, an eastbound flight across six time zones and a

westbound flight across six time zones. The shaded area to the left of each graph shows sleep prior to the transmeridian flight and extends backward in time for three days. The shading on the time scale shows when it will be dark or light at each location; the time scale is for Base time (CST). Flying west the daylight is increased on Thursday; flying east it is reduced. Effectiveness is 97 % upon arriving to work on the first day in the new time zone for westward travel; it is 85% for eastward travel.

Note that predicted performance while awake is more disrupted for a longer period of time by the eastbound flight compared to the westbound flight. This is a commonly reported difference in "jet lag" for east and west plane travel (Klein and Wegman, 1980; Haus and Halberg, 1980). These effects on performance are a logical and inherent outcome of the interplay of the various processes in the model and did not require a special "jet lag" algorithm. The only fundamental change in the SAFTE model was the logic to detect the change in the sleep/work pattern and to readjust the phase of the circadian rhythm to the new work pattern indicative of the shift in time zone. The performance prediction was a natural outgrowth of the shifting circadian phase.

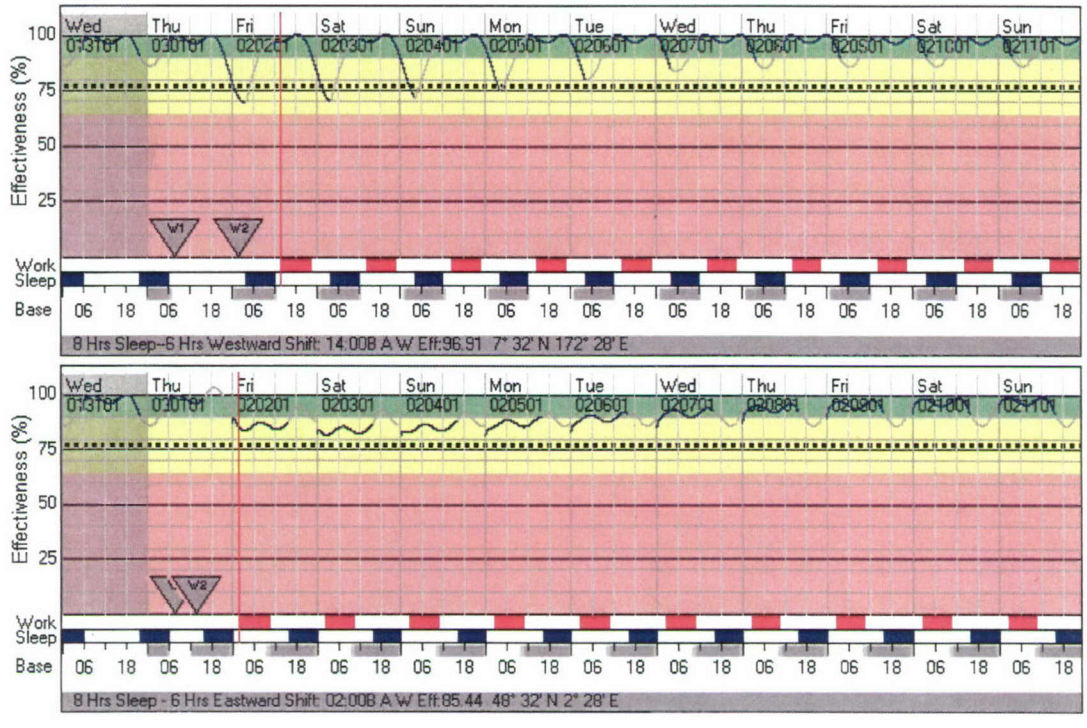

Figure 11. This FAST™ graph shows the performance effects of westward and eastward travel across 6 time zones. Top Graph: W1 shows departure from San Antonio, Texas; W2 is arrival in Majuro. Work starts in Majuro at 1400 San Antonio time. Bottom Graph: Departure from San Antonio, Texas and arrival in Paris. Work starts in Paris at 0200 San Antonio time.

Subtask 1.3. Countermeasures Effects on Performance

This task was to develop the stimulant and sleep aid parameters for SAFTE. Stimulant parameters were developed for SAFTE, but sleep aid parameters were not because our Sleep

Aids Study showed no effect of sleep aids on cognitive performance at night. In other words, we had no sleep aid effect to model (Eddy, Cardenas, French, Gibbons, Miller, Ramsey, & Storm, 2005, in preparation). Although we have developed an algorithm for including stimulant parameters into the SAFTE model, additional data are needed to validate the parameters estimated from Pigeau, Naitoh, Buguet, McCann, Baranski, Taylor, Thompson, and Mack (1995).

Pigeau, et al. conducted a study of modafinil, dextroamphetamine and placebo during 64 hours of sustained mental work and collected cognitive performance data from their participants. Based the data from their published, SAFTE has a stimulant fatigue countermeasure algorithm that predicts the performance effects of d-Amphetamine (20 mg) and Modafinil (300 mg). Army researchers at WRAIR have collected additional data and it is hoped that these data can eventually be used to validate the SAFTE stimulant algorithm.

Based on this published study of modafinil and dextroamphetamine effects during sleep deprivation, Pigeau, et al. (1995), Hursh has proposed an innovative model of stimulant effects that may be incorporated into any fatigue model. The basic concept of the drug effects model is illustrated in Figure 12. The fine line in the figure represents performance during sleep deprivation without the stimulant – placebo (P). The dark line represents performance under the effect of a stimulant drug (D). Both are normalized to baseline, defined as 1.0. We define two measures: 1) the fatigue effect (1-P), the difference between baseline performance and fatigued performance (P), and 2) the drug effect (D-P), the amount of improvement in performance induced by the drug. We define a variable designated as the proportional drug effect (PDE) as the ratio of these two measures:

Equation 5. $PDE = (D-P) / (1-P)$

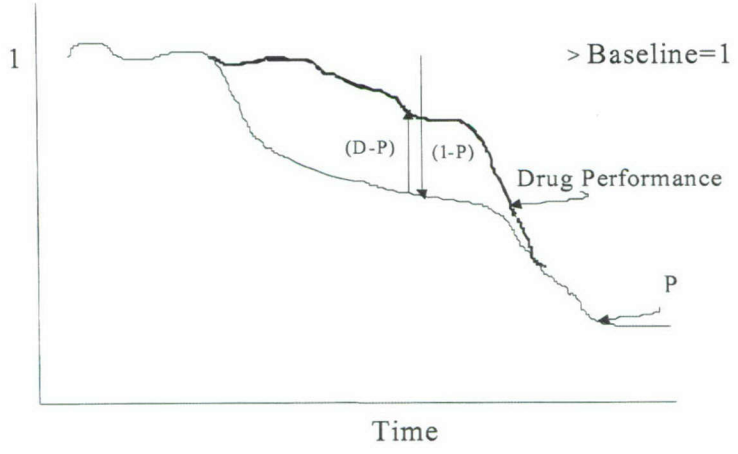

Figure 12. Basic components of a stimulant drug effect on performance.

Based on the Pigeau, et al. (1995) data, PDE was computed for the average performance under d-Amphetamine (20 mg) and Modafinil (300 mg). The change in PDE was fit by a two-phase exponential function as shown in Figure 13.

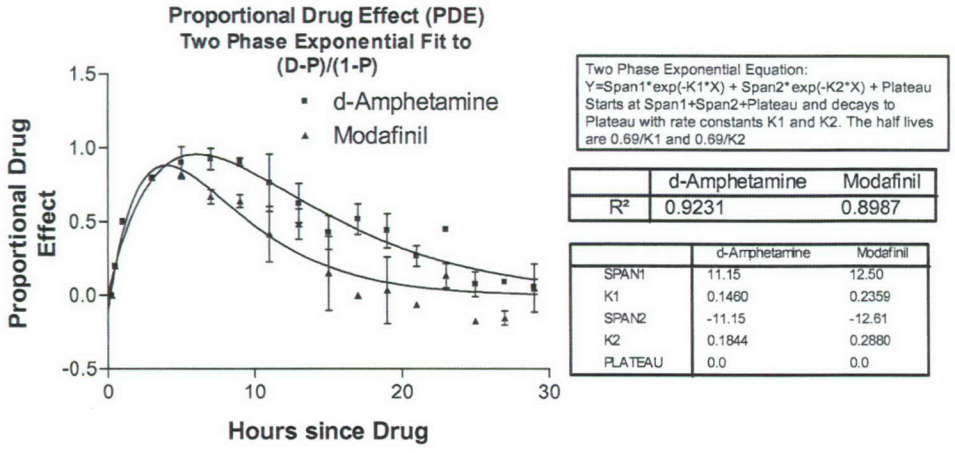

Figure 13. Two-phase exponential representation of the proportional drug effect.

Using this basic representation of the drug effect, we compute a transform of predicted effectiveness from the SAFTE fatigue model as follows:

- PDE is defined as above.
- MaxDE is the maximum effectiveness under drug, which was 0.93 based on Pigeau, Naitoh, Buguet, McCann, Baranski, Taylor, Thompson, and Mack (1995).
- PE is placebo or non-drug effectiveness predicted by the base fatigue model.
- Effectiveness under drug, then, is modeled as the following:

Equation 6. Drug Effectiveness = (MaxDE) * (PDE) + (1 - PDE) * (PE)

This quantity ranges from MaxDE to PE during course of drug effect. The virtue of this representation is that it will not exceed some maximum reasonable performance and the drug effect on performance dissipates according to the two-phase exponential function used to represent PDE. In essence, the drug model is a two-state model represented by MaxDE and PE (maximum drug effect and placebo effect) that transition from the PE state to the MaxDE state and back to the PE state according to the exponential model of drug uptake and elimination (PDE).

Using the SAFTE model as the base fatigue model, we combined this stimulant model with the predicted fatigue effect, illustrated in Figure 14.

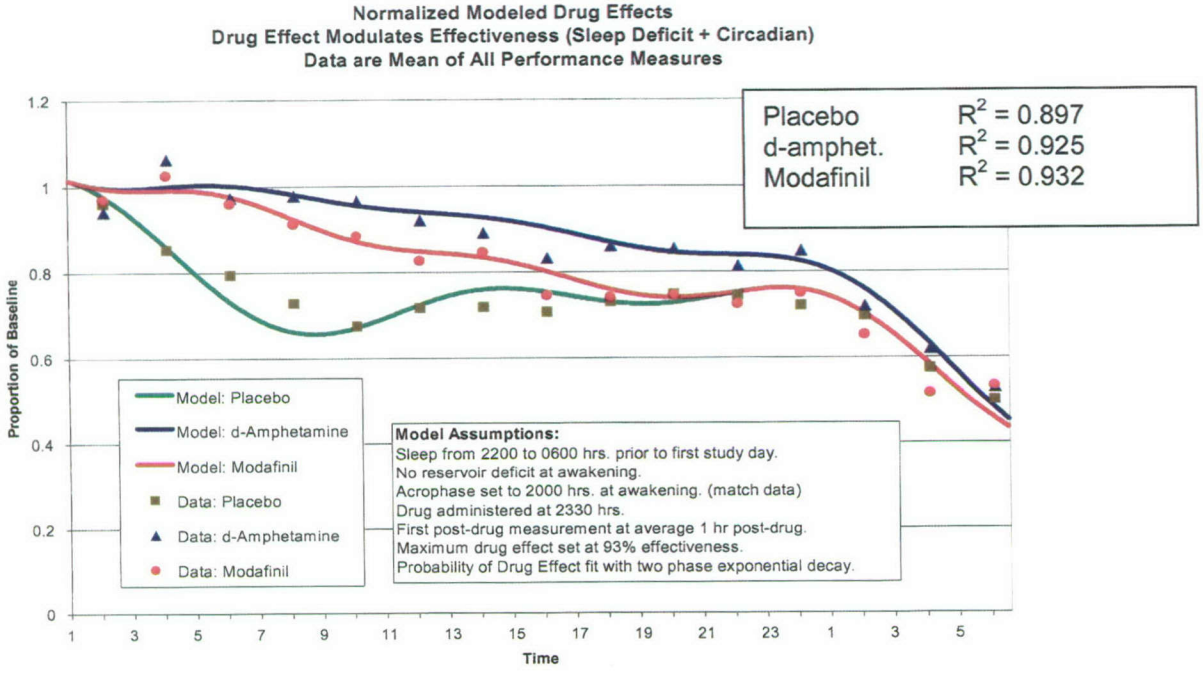

Figure 14. Predicted performance using the SAFTE model combined with the stimulant model.

The data shown in Figure 14 are from Pigeau, et al. (1995). The base fatigue model predictions with and without drug effect were fit to these data and the R^2 for the three groups ranged from 0.90 to 0.93. The parameters for the two-phase exponential representations of d-amphetamine and Modafinil are shown in Figure 13.

While this model of stimulant effects appears promising, it is incomplete. Most important, this model does not represent the detrimental effects of either drug on the ability of a person to sleep. Any complete model of a stimulant effect on performance to counter fatigue must also represent the possible negative effects of retarding or preventing recovery sleep. The next step in the validation process would be to use existing data from Wesensten, Killgore & Balkin (2004) conducted at the Walter Reed Army Institute of Research to validate the method for the stimulant effect on performance. This study examined amphetamine, modafinil, and caffeine effects on performance during sleep deprivation. Additional studies conducted at the Air Force Research Laboratory (AFRL) and WRAIR could be used to refine and validate the method. In addition, we could refine the parameters of the two-phase exponential to represent various doses and an additional compound, caffeine. Based on each stimulant's serum half-life, we would approximate each stimulant's effect on recovery sleep and subsequent post sleep performance. Any new studies published between now and this additional modeling work would be used to inform and constrain the recovery sleep and subsequent performance effects. We would also recommend conducting one or more studies of stimulant effects with appropriate measures of sleep latency, quality and quantity to completely validate both sides of the stimulant "equation."

We have also developed an extension of this model for multiple drug deliveries. The current model can handle up to *four* sequential drug administrations within a 28 hr period (maximum drug effect duration). The model maintains a running proportional drug effect (PDE) from each drug administration and computes a total drug effect that is the combined probability of being affected by the first, second, third, or fourth drug administration: $1-[(1-f_a)(1-f_b)(1-f_c)(1-f_d)]$. Figure 15 shows the effects of two days of three sequential doses of d-amphetamine at 0000, 0400, and 0800 hrs. Maximum drug effect was assumed to be 98% effective. These results compare favorably to the graph of results in Caldwell, Smythe, Leduc, and Caldwell (2000) and Caldwell and Caldwell (1997); however, a statistical comparison cannot be performed without the actual data.

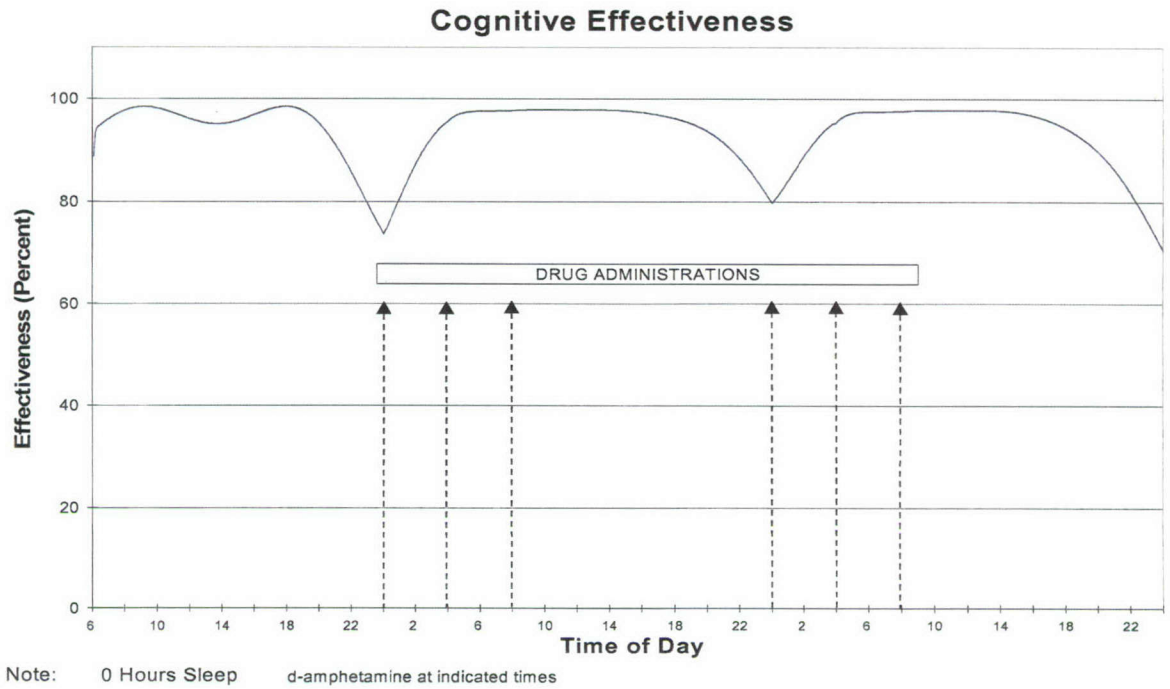

Figure 15. Predicted results with multiple drug deliveries.

Like the method used for stimulants, a similar strategy may be applied to the problem of representing sedative effects. In this case, the primary effect may be represented as an effect on the rate of accumulation of sleep benefit into a sleep reservoir, in the terminology of the SAFTE model, or on the sleep hemostat as defined for other fatigue models (see Akerstedt & Folkard, 1991; Folkard & Akerstedt (1987). The effect of a sedative may be to temporarily enhance the rate of elimination of sleep debt, thus improving subsequent performance. A similar two-phase exponential may be used to represent the shift from a baseline rate of recovery to an enhanced rate of recovery and then back to baseline as the drug effect dissipates. As with the representation of stimulants, the direct effects of the sedative on performance would also have to be represented for the model to be complete. Sedatives are known to have sizeable detrimental effects on cognitive performance (Whitmore, Fischer, Barton, & Storm, 2004; Storm, Eddy, Cardenas, Hickey, Ramsey & Welch, 2004) and this side effect must be part of the overall sedative "equation."

Subtask 1.4. Sleep Timing Algorithm

This subtask was designed to create an additional capability within SAFTE and FAST™ to predict the time and amount of sleep when the exact or expected information was unknown. Because no data were available to compute an algorithm for estimating when pilots sleep for various missions (Task 5), data from train engineers working on various schedules were used. An Autosleep algorithm using these data was developed that estimates when an engineer sleeps for working a particular work schedule. This algorithm is consistent with the findings of Foret and Lantin (1972), who also collected data from train engineers working irregular schedules. This algorithm is implemented in FAST™ and is not a part of the SAFTE model as it was originally conceived in the Phase 2 proposal. Subtask 2.4 below describes the development of the algorithm for automatically inserting sleep into a work schedule using FAST™.

Task 2 Results: Refinements to FAST™

In addition to the FAST™ improvements called out in the Phase 2 proposal the following capabilities were also added to FAST™:

- Tabular data entries of sleep and work intervals.
- An event marker capability for either critical events or waypoints or both.
- Sleep quality with four levels.
- An optional blood alcohol concentration level axis.
- An optional continuous acrophase line spanning the entire schedule.
- An optional continuous sleep reservoir line spanning the entire schedule.
- An optional percentile line graphically displaying a selected percentile to the user.
- An undo button.
- Selectable tables of the schedule's sleep, awake, and work intervals, and of event markers.
- A summary table containing the schedule attributes
- Selectable graph ordinate starting from 0 to 50%

Further information on each of these items can be found in the Startup Guide for FAST™ and will not be described in this report. Additional FAST™ features, also not originally proposed, are described in the report when they are closely related to the SBIR funded work.

Subtask 2.1. Mission Timeline

In addition to the above listed FAST™ enhancements a mission timeline was added as an output option to FAST™. Once selected from the print menu, the user has the option of choosing any of the following variables to produce a printed document organized by either 30-minute or 1-hour time blocks:

- Day number
- Date
- Base time
- Zulu time

- Mission elapsed time
- Latitude and longitude
- Light level
- Performance effectiveness
- Sleep state
- Work state
- Events

Figure 16 shows a time line from New York to Rome, blocked in 60-minute intervals. To conserve space only the take-off, landing and one additional day are shown. The latitude and longitude between waypoints that was recorded in the event markers are interpolated and should not be used for navigation. The Light column displays periods of light and dark throughout the mission, which are especially helpful to pilots both planning and executing their missions. The light levels are computed from algorithms described by Van Bochove (1982). Three levels of darkness are shown graphically at sunrise and sunset throughout a schedule. This illumination information is used in SAFTE to compute the effects of light on resetting the circadian rhythm as described in Subtask 1.2, Transmeridian Adjustment. The performance effectiveness column is color-coded corresponding to the levels set by the user in the FAST™ graphical display

Base: unknown
Mission: unknown
Start: <NEW YORK CITY NY KENNEDY: JFK>Depart New York 01/03/00 08:01
End: 01/04/00 17:15 Timeline End 01/04/00 16:01

Day	Date	Base	Zulu	Loc	Light	Eff	Sleep	Work	Events
2	01/03/00	08:00	13:00	40° 39' N 73° 47' W	1.00	99.49	0.00	0.00	08:00 <NEW YORK CITY NY KENNEDY: JFK>Depart New
2	01/03/00	09:00	14:00	44° 28' N 64° 37' W	1.00	99.72	0.00	0.00	
2	01/03/00	10:00	15:00	47° 28' N 54° 20' W	1.00	99.33	0.00	0.00	
2	01/03/00	11:00	16:00	49° 26' N 43° 1' W	1.00	98.45	0.00	0.00	
2	01/03/00	12:00	17:00	50° 14' N 31° 4' W	0.82	97.41	0.00	0.00	
2	01/03/00	13:00	18:00	49° 47' N 19° 1' W	0.16	96.58	0.00	0.00	
2	01/03/00	14:00	19:00	48° 8' N 7° 29' W	0.00	96.28	0.00	0.00	
2	01/03/00	15:00	20:00	45° 24' N 3° 7' E	0.00	96.66	0.00	0.00	
2	01/03/00	16:00	21:00	41° 48' N 12° 36' E	0.00	97.62	0.02	0.00	16:00 <ROME ITALY: FCO>Arrive Rome
2	01/03/00	17:00	22:00	41° 48' N 12° 36' E	0.00	99.79	1.00	0.00	
2	01/03/00	18:00	23:00	41° 48' N 12° 36' E	0.00	102.36	1.00	0.00	
2	01/03/00	19:00	00:00	41° 48' N 12° 36' E	0.00	103.69	1.00	0.00	
2	01/03/00	20:00	01:00	41° 48' N 12° 36' E	0.00	103.59	1.00	0.00	
2	01/03/00	21:00	02:00	41° 48' N 12° 36' E	0.00	102.09	1.00	0.00	
2	01/03/00	22:00	03:00	41° 48' N 12° 36' E	0.00	99.55	1.00	0.00	
2	01/03/00	23:00	04:00	41° 48' N 12° 36' E	0.00	96.57	1.00	0.00	
3	01/04/00	00:00	05:00	41° 48' N 12° 36' E	0.14	93.80	0.98	0.00	
3	01/04/00	01:00	06:00	41° 48' N 12° 36' E	0.64	89.12	0.00	0.00	
3	01/04/00	02:00	07:00	41° 48' N 12° 36' E	1.00	87.00	0.00	1.00	
3	01/04/00	03:00	08:00	41° 48' N 12° 36' E	1.00	84.95	0.00	1.00	
3	01/04/00	04:00	09:00	41° 48' N 12° 36' E	1.00	84.26	0.00	1.00	
3	01/04/00	05:00	10:00	41° 48' N 12° 36' E	1.00	84.72	0.00	1.00	
3	01/04/00	06:00	11:00	41° 48' N 12° 36' E	1.00	85.82	0.00	1.00	
3	01/04/00	07:00	12:00	41° 48' N 12° 36' E	1.00	86.99	0.00	1.00	
3	01/04/00	08:00	13:00	41° 48' N 12° 36' E	1.00	87.74	0.00	1.00	
3	01/04/00	09:00	14:00	41° 48' N 12° 36' E	1.00	87.80	0.00	1.00	
3	01/04/00	10:00	15:00	41° 48' N 12° 36' E	0.89	87.20	0.00	0.00	
3	01/04/00	11:00	16:00	41° 48' N 12° 36' E	0.39	86.21	0.00	0.00	
3	01/04/00	12:00	17:00	41° 48' N 12° 36' E	0.00	85.25	0.00	0.00	
3	01/04/00	13:00	18:00	41° 48' N 12° 36' E	0.00	84.74	0.00	0.00	
3	01/04/00	14:00	19:00	41° 48' N 12° 36' E	0.00	84.95	0.00	0.00	
3	01/04/00	15:00	20:00	41° 48' N 12° 36' E	0.00	85.91	0.00	0.00	
3	01/04/00	16:00	21:00	41° 48' N 12° 36' E	0.00	87.31	0.02	0.00	16:00 01/04/00 17:15 Timeline End

Figure 16. This image shows an example timeline output from FAST™. In addition to the columns displayed, the user may also add elapsed time. With a take-off at 0800, notice the night starts on Day 2 at 1400 when flying east, resulting in a shortened day.

The printed timeline can be scaled to fit on paper stock of different sizes. This allows a schedule to be customized to fit a pilot's kneepad.

Subtask 2.2. Alternative Populations and Performances

Subtask 2.2 is the FAST™ implementation of the completion of Subtask 1.1 in SAFTE. Although we were unable to model pilot performance under fatigue due to corrupted data in the French, Neville, Eddy, Storm, Cardenas, & Flynn (2006) study, we have been able to model a specific task used to measure the effects fatigue, the Psychomotor Vigilance Task (PVT). In addition we have implemented a visual cue on the graphical display that represents predictions for percentiles other than the 50th. This gives the user an indication of the variability or error of performance prediction.

Lapse Index. Data from the Army's dose-response study were used to create an algorithm for deviation from baseline for reciprocal reaction time and for lapses in the PVT. The lapse index can be turned on or off by checking the lapse index on the Graphic Display pull-down menu. Lapses for a rested person are usually 1 or fewer for a 10-minute PVT. Therefore, one can read the FAST™ Lapse index as a fatigue gauge that quantifies the likelihood of making a lapse relative to that of a fully rested person. That is, if FAST™ projects six lapses for the time period of some critical task, then one should interpret this as meaning that the person will be six times as likely to have a lapse as when rested. Figure 17 shows the Lapse Index displayed from the FAST™ schedule from which the NY to Rome timeline was created. Notice the negative correlation between performance effectiveness and the lapse index.

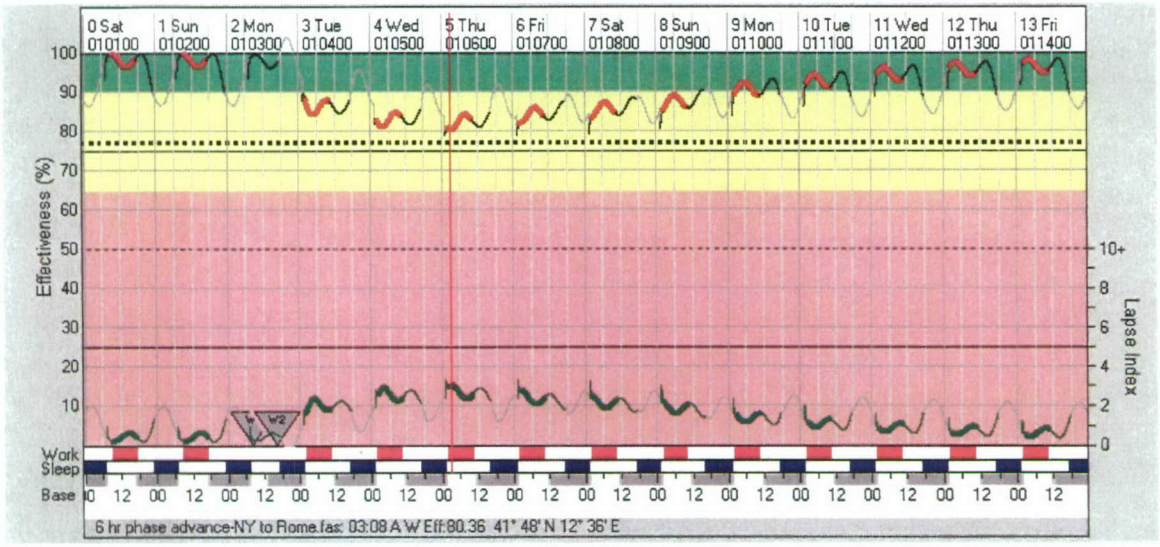

Figure 17. FAST™ display with Lapse Index enabled. Notice that performance is actually worst the third day after arriving at the destination on this eastbound schedule.

Representations of Performance Variability. In practice, a fatigue model may be applied to two general problems. The first is the design and planning of operations for a group of individuals. The model may be used to plan for sleep periods and countermeasures to maintain acceptable performance of the group. The second is the analysis of individual readiness to perform a mission, either prior to an operation or as a retrospective analysis after an error or accident. Many fatigue models predict the average performance of adults as assessed using tests of vigilance or cognitive throughput. Based on a limited sample of participant data, FAST™ was enhanced to allow SAFTE to predict group variance around the mean. No model can predict the unique performance of an individual because individuals vary in their sensitivity to the effects of

sleep deprivation or restriction. For example, in the SDR study described previously, the 3-hour TIB group showed a considerable amount of variance in performance at the end of the test week; mean speed on the PVT for individual subjects ranged from 80% to 20% of baseline. In addition, variability between participants increased across the week of sleep restriction. Given this variability, any model that predicts average performance, even if it is very accurate, will have an inherent error when applied to any particular individual because of the individual differences in sensitivity to sleep deprivation.

This limitation presents difficulties for the two major applications of fatigue models. First, designing a mission based on mean group performance may not provide a sufficient amount of sleep to maintain adequate performance for a significant minority of the group. Second, individual readiness can deviate dramatically from that of the average person and individuals may be inappropriately labeled as fatigued who are very capable of adequate performance.

One approach to model prediction error, especially when models are used to plan missions for groups of individuals, is to calculate the standard deviation of group performance and plot that error range along with the mean prediction. SAFTE and FAST™ were extended to implement that idea. We began by carefully analyzing the data from the 3-hr, TIB group in the Walter Reed study described above and removed the data of one subject who we classified as an outlier. According to the FAST™ predictions for these data, sleep debt increases progressively during the week of sleep restriction. We determined that the group standard deviation of PVT speed was directly related to the number of days of sleep restriction and accumulated sleep debt, as one might expect if individuals differ in sensitivity to restricted sleep. A sigmoid function was used to model this relationship with reasonable accuracy. In this simple sub-model, sleep debt (SD, here represented as the ratio of the current level of the internal reservoir relative to its full capacity) is treated as the fundamental driver of between subject variance in performance.

Equation 7. $STDEV = 1 / (2 + EXP(a * SD + b))$

Where: SD = Reservoir Fraction (ratio of current value to capacity),
STDEV = Standard deviation expressed as ratio of mean throughput (speed),
a = 13.48615, and
b = -7.83688

This standard deviation model is depicted in Figure 18. As the sleep reservoir in the model depletes, moving from left to right on the abscissa, the predicted standard deviation of the group throughput or speed increases. We represent the standard deviation as a fraction of the mean value; hence, a value of 0.5 means that the standard deviation is half the mean value. The computed values fit both the absolute throughput change scores and the normalized throughput changes (differences from baseline). Since the SAFTE model predicts changes relative to a fully rested baseline performance, the normalized throughput version has been incorporated into SAFTE/FAST™.

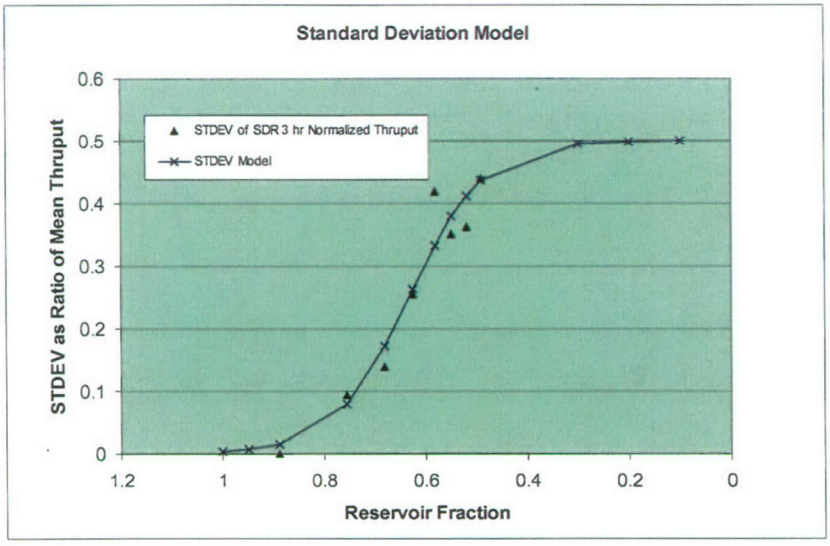

Figure 18. Standard Deviation Model and standard deviation data.

Figure 19 shows how the standard deviation prediction overlays with the individual participant data for the 3-hr TIB group. The triangles and diamonds represent the lower and upper standard deviations, respectively. Within FAST™, we use these standard deviations to compute percentile lines that can be plotted along with the mean; for example, a line can be plotted that shows the lower 20% of the population. This allows the user to estimate a range of predictions and the proportion of the population that it would represent. As far as we know, this is the only algorithm available within a fatigue model that incorporates an estimate of prediction error resulting from between subject variance.

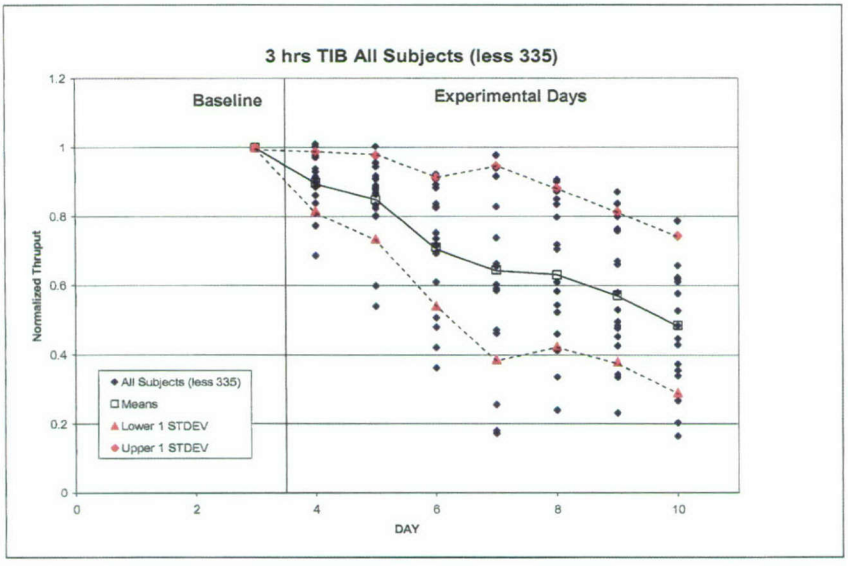

Figure 19. Standard deviation predictions and individual subject data

While promising, the current variance model is based entirely on this group of sixteen participants from the Army study. This computation needs further refinement with additional data from Army and AF laboratory experiments. Figure 20 shows a FAST™ graph for a counter-clockwise shift rotation with the 20th percentile represented with a dashed line on the standard FAST™ graph. At the lowest point of the night, the average person is degraded to 63% effectiveness, but the 20th percentile person is nearly 8% worse.

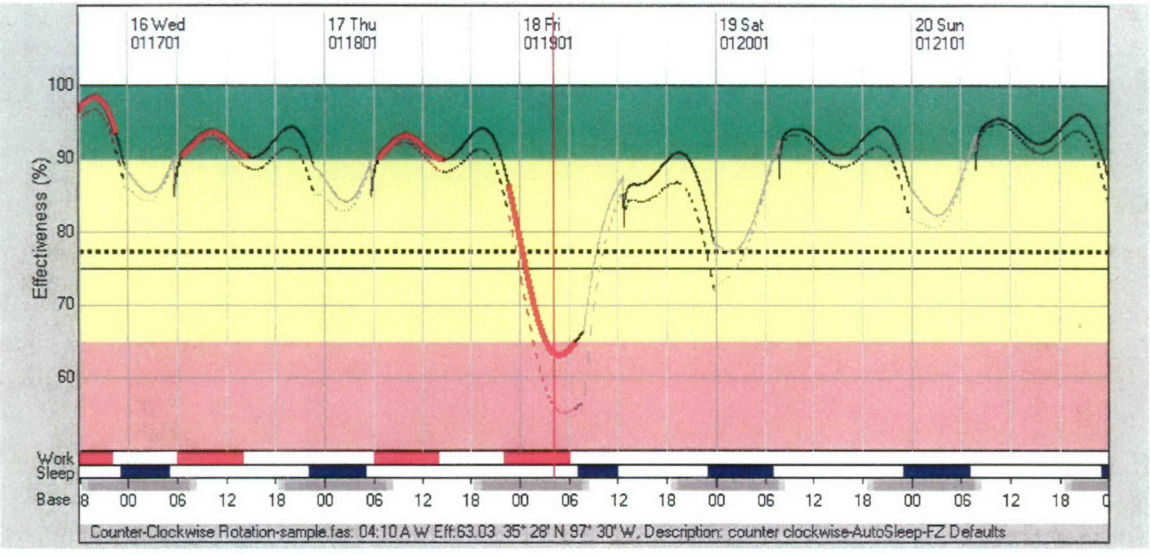

Figure 20. This is a FAST™ graph showing performance predictions for a shift from morning work to a midnight shift for individuals at both the 50th percentile (solid line) and the 20th percentile (dashed line). This graph also has the ordinate starting at 50% instead of 0%.

Subtask 2.3. Use and Effects of Fatigue Interventions

No algorithms for the use of pharmaceutical fatigue countermeasures have been incorporated in FAST™ at this time. A stimulant effect option will be added when the algorithm in SAFTE has been validated with data independent of the algorithms creation. Although the stimulant and sleep aid effect predictions could not be implemented in FAST™, additional countermeasures prompts were added to aid a user in making a decision to use a fatigue intervention. This section describes the addition to FAST™ of a user-selectable limit that is displayed graphically warning of unacceptable performance degradation, of statistical data indicating the magnitude of the degraded performance exceeding the user-selected limit, and of a dashboard of commonly accepted fatigue indicators.

Criterion Line. This dashed horizontal line shown in Figure 20 divides the Yellow Zone in the middle of the FAST™ graph (default 77.5%) and is a guide for using countermeasures to enhance performance. Performance in the yellow zone below the criterion line represents the performance of a person during the day following loss of an entire night's sleep. A user can adjust this line to a level that is appropriate for the risk associated with the job being scheduled. The criterion line would be set high, say 90%, for piloting an aircraft, whereas it might be set at 70% for completing insurance forms or sorting parts into bins. In either case once performance was projected to fall below the line, some fatigue countermeasure would be taken.

Statistical Data in the Summary Tables. The FAST™ Summary Tables now include a column that indicates the percent of time Below the Criterion Line (BCL) as an easy method for comparing amounts of poor performance across schedules. This statistic is available for the summary statistics for work intervals and awake intervals. Table 3 shows a section of the FAST™ work summary table from the schedule in Figure 20. For the shift ending on Friday 19 January, 79.58% of the work period was projected to be Below the Criterion Line of 77.5% effectiveness.

Table 3. Work Summary for Counter-Clockwise Shift Change shown in Figure 20.

Start			End			Stats		
Day	Date	Time	Day	Date	Time	Duration (Minutes)	Performance Effectiveness	%BCL
Mon	01/15/01	14:00	Mon	01/15/01	21:59	480	95.56	0.00
Tue	01/16/01	14:00	Tue	01/16/01	21:59	480	96.41	0.00
Wed	01/17/01	06:00	Wed	01/17/01	13:59	480	92.27	0.00
Thu	01/18/01	06:00	Thu	01/18/01	13:59	480	91.80	0.00
Thu	01/18/01	22:00	Fri	01/19/01	05:59	480	69.85	79.58
Mon	01/22/01	08:00	Mon	01/22/01	15:59	480	95.22	0.00
Tue	01/23/01	08:00	Tue	01/23/01	15:59	480	96.15	0.00

Dashboard. A panel or Dashboard may now be displayed in FAST™ on the schedule screen. It displays a summary of performance effectiveness and fatigue factors at the point of the cursor in the schedule. By clicking on the Details bar on the Dashboard, a table is displayed that gives five performance metrics and five fatigue factors calculated for the selected time point in the schedule, as shown in Figure 21 (Note: for this example, the red zone was set to start at 70%, see Graphical Display, Zone Limits). The menu has options for copying the Dashboard display to the clipboard for pasting into documents or printing (also activated by a right mouse click on the dashboard display).

Performance Metrics: The performance metrics on the left side of the Dashboard are:

- Effectiveness, a score based on predicted speed on a psychomotor vigilance test (PVT).
- Mean Cognitive, a score that approximates the average cognitive throughput on standard cognitive tests (average speed of mental operations as a percent of rested performance).
- Lapse Index, a value that represents the likelihood of a lapse in attention relative to a well-rested person.
- Reaction Time, a value that is the average reaction time, expressed as a percent of the average reaction time of a well rested person.
- Reservoir, the current level of the sleep reservoir expressed as a percent of the full capacity.

Fatigue Factors: On the Right side of the Dashboard are the fatigue factors for the selected time point in the schedule and the criterion values that are considered by experts to increase the risk of errors (far right column, in grey):

- Recent Sleep in the Last 24 hrs, which is the total number of hours in the previous day.

- Chronic Sleep Debt, which is the cumulative number of hours of sleep that have been missed since the last time the sleep reservoir was full.
- Hours Awake, which is the number of continuous hours since the last period of sleep.
- Time of Day, which is an evaluation of vulnerability to error based on the person's own adjusting circadian rhythm. For a person with a normal bedtime of 2300 hrs, maximum vulnerability is considered to be between midnight and 0600 hrs in the morning. Times are shown in Base Time but are always adjusted to the person's own rhythm.
- Out of Phase, which is a measure of the degree of desynchronization of the person's own circadian rhythm relative to the optimal phase for the current pattern of sleep and wakefulness, measured as the number of hours out-of-phase – a measure of "jet lag" or "shift lag."

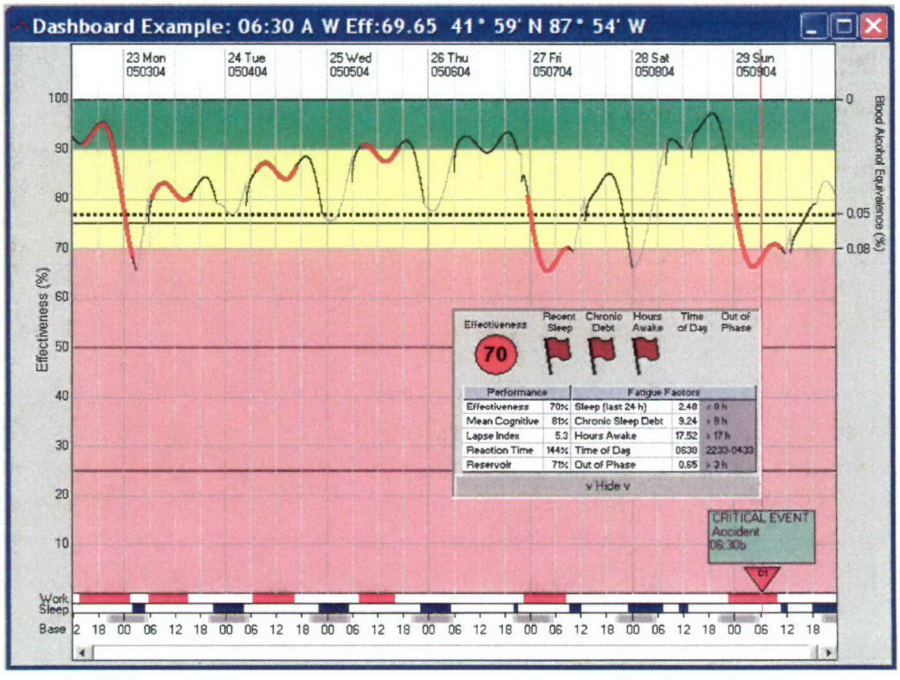

Figure 21. This graph shows the Dashboard at the critical time of a railroad accident. Three fatigue factors are indicated and a performance effectiveness of 70 is below the criterion line, which was set at the performance equivalence of 0.05% blood alcohol concentration, 77.5%.

Subtask 2.4. Sleep Schedule and Typical Schedule Generation

The goal of this task was to design an algorithm that would create sleep periods for a work schedule that mimic what might be expected of an actual person preparing for such a schedule. Since no sleep data were available for pilots, we used data available to us from railroad engineers. The approach taken was to find parameters that would allow the algorithm to closely match sleep as recorded by actual engineers using sleep logs. The algorithm was not designed to create an "optimal" sleep schedule that would maximize performance, but one that would predict regular "typical" patterns of sleep. The algorithm would not predict idiosyncratic patterns unrelated to the work schedule nor was it designed to insert extra naps into the schedule that

would anticipate evening work starts following a normal night of sleep. These can be inserted manually. A limitation of the algorithm that resulted from the data set upon which it was built was that it would not be able to predict sleep when crossing multiple time zones. A more general algorithm of this type would require data from individuals with schedules crossing multiple time zones.

The data used as the basis for generating the sleep rules was constrained by the following:

- Engineers average a little over 7 hours of sleep per day.
- Engineers work about 8 hours per day on average.
- Engineers who end work between 0500 and noon get a little over 5 hours of sleep in 24 hours, except for work end times between 0800 and 0900 (optimal split sleep work end time) when they get 6 hours of sleep as shown in Figure 22.
- Engineers who end work between 1500 and 0100 get about 8 hours of sleep.
- In the data we examined, there was no consistent relationship between the geographic location of sleep and sleep duration or quality.
- Engineers seldom slept between noon and 2000 hours (8 pm) – "forbidden sleep zone" as shown ir

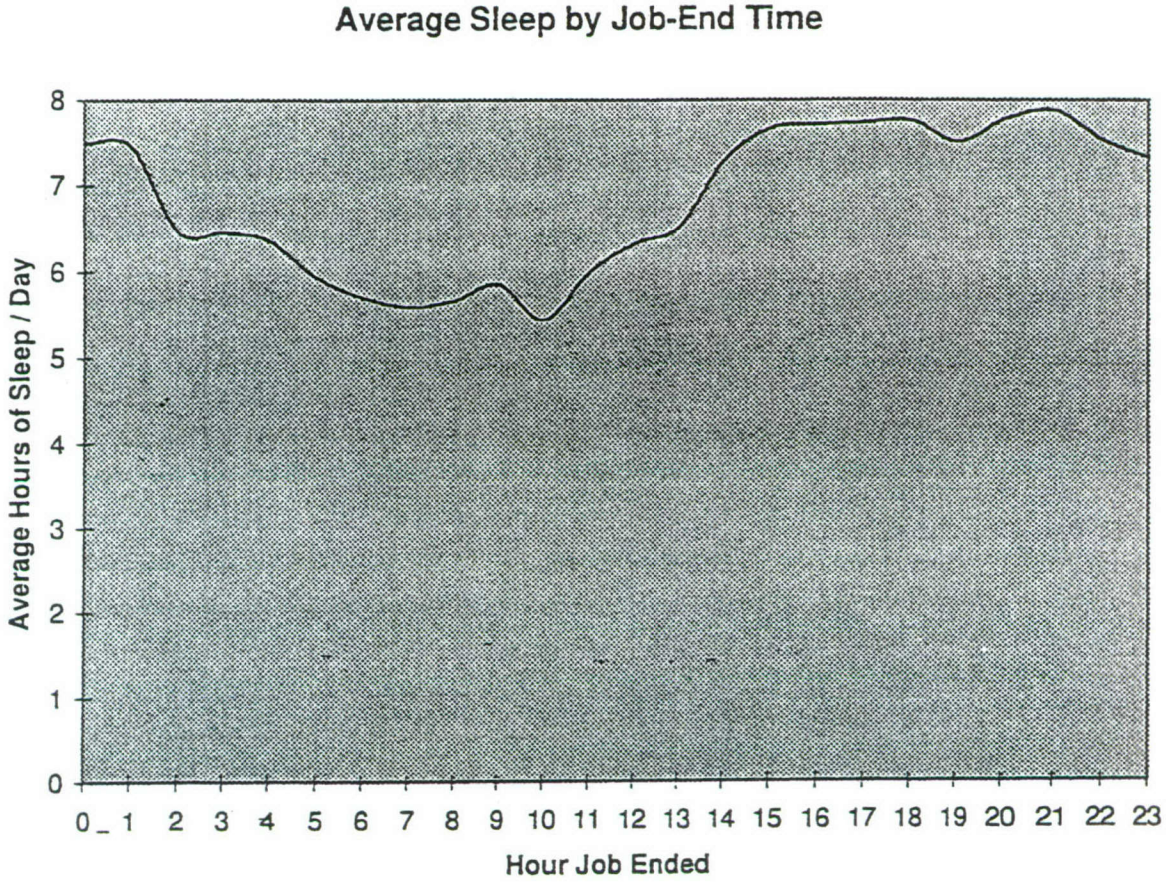

Figure 22. Railroad engineers often sleep less than 8 hours when their work ends between 0200 and 1300. Taken from Pollard, (1996).

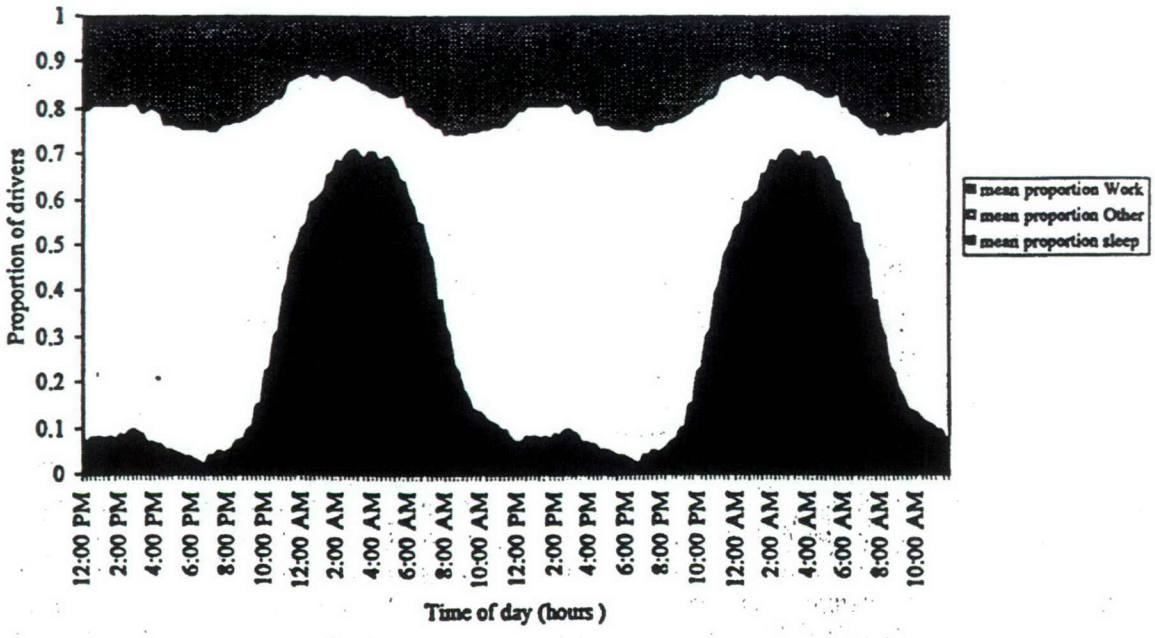

Figure 23. This figure was reproduced from Reid, Roach & Dawson (1997) and shows the proportion of time railroad engineers spend sleeping and working irregular hours across the day.

The "Forbidden Zone" for sleep in train engineers was not an unusual finding. Both Reid, et al. (1997) and Foret & Lantin (1972) found that engineers seldom sleep during the afternoon independent of when called for work. Although sleep may occasionally occur during this period, a regular pattern emerges that suggests that the usual preference is to remain awake during this period.

From these data two sleep rules emerged.

- Rule 1: Start Sleep Early - Work ends in first half of day between midnight and 1200 and first sleep period starts early (work end plus commute time) and continues until 8 hours have accumulated. Sleep is split, if necessary, to avoid the "forbidden zone" from 1200 to 2000 (also, see minimum sleep period rule, below). For work end times in the morning, 8 hours of sleep cannot be accumulated because of conflict with the "forbidden zone."
- Rule 2: Delay Sleep to Evening - Work ends in afternoon during the "forbidden zone" (1200 to 2000) or in the evening between 2000 and midnight. Sleep is delayed at least until after the forbidden zone or until normal bedtime, nominally set at 2300. Sleep continues until 8 hours have accumulated. For work end times in first half of this period, 8 hours may not be achieved because of the likely early morning call between 0400 and 0700.

General Rules

- Commute Time: Always allow commute time between work end and any possible sleep start (nominally 1 hour) and commute time between sleep end and any possible work start (again, nominally 1 hour).
- Minimum Sleep Period: A sleep period will not be scheduled for less than 1 hour.

- Default or "Rest Day" Sleep: Any day that has no work after 12 noon qualifies for default sleep starting at normal bedtime. This rule "fills in sleep" on rest days and sleep is according to "rest day" rules. For example, if work ends at 0600 on Friday and resumes again on Monday morning at 0700, then rest day sleep would be scheduled for Friday, Saturday, and Sunday night. If work ends after noon on Friday, then sleep on Friday would be according to Rule 2 (above) and sleep on Saturday and Sunday would be rest day sleep. Nominal sleep on rest days is 8 hours but can be set longer (or shorter) than for workdays.
- Maximum Sleep per Day: the rules are coordinated such that no more than the maximum amount of work day sleep (nominally 8 hrs) will occur on a calendar day in which work occurs.

Sleep Time Calculation Rules

- Rule 1 – Start Sleep Early, Split Sleep if Necessary:
- For Work End (WE) = 0000 to 1159
- Start next sleep period at WE + Commute Time (adjustable)
- Sleep until next Work Start – Commute Time or until cumulative sleep = 8 hours (adjustable)
- Except times = 1200 to 2000 (forbidden zone, adjustable)
- Minimum sleep period = 1 hour (adjustable)
- Rule 2 – Delay Sleep to Evening:
- For WE = 1200 to 2359
- Delay start of next sleep period at least until the end of the forbidden zone (sleep delay) or until normal bedtime (adjustable), whichever is earlier.
- Sleep Delay = Time of Forbidden Zone End – 1200 hrs
- If work ends after normal bedtime, sleep starts immediately after commute time (adjustable)
- Sleep until next Work Start – Commute Time or until cumulative sleep = 8 hours (adjustable)
- Minimum sleep period = 1 hour (adjustable)

Sample Sleep Calculations are shown in Table 4. The table shows the conditions that must be met to insert sleep at specific times and for specific durations. The durations are of course reduced by commute times and work intervals.

Table 4. Sleep Calculation Rules

Rule	WE	Next WS	Sleep	Sleep Duration
Rule 1: 2200 to 1159	0000	1600	0000-0800	8
Early Morning Sleep	0100	1700	0200-1000	8
	0200	1800	0300-1100	8
	0400	2000	0500-1200	7
	0500	2100	0600-1200	6
	0600	2200	0700-1200	5
Split Sleep	0700	2300	0800-1200 2000-2200	6
	0800	0000	0900-1200 2000-2300	6
	0900	0100	1000-1200 2000-0000	6
Early Evening Sleep	1000	0200	2000-0100	5
	1100	0300	2000-0200	6
Rule 2: 1200 to 2159	1200	0400	2000-0300	7
Night Sleep	1400	0600	2200-0500	7
	1500	0700	2300-0600	7
	1600	0800	2300-0700	8
	1800	1000	2300-0700	8
	2300	1500	2400-0800	8
Note: Assume 16 hours from Work End (WE) to Next Work Start (WS).				

Figure 24 shows the probability for generating sleep for each hour in a day using the rules.

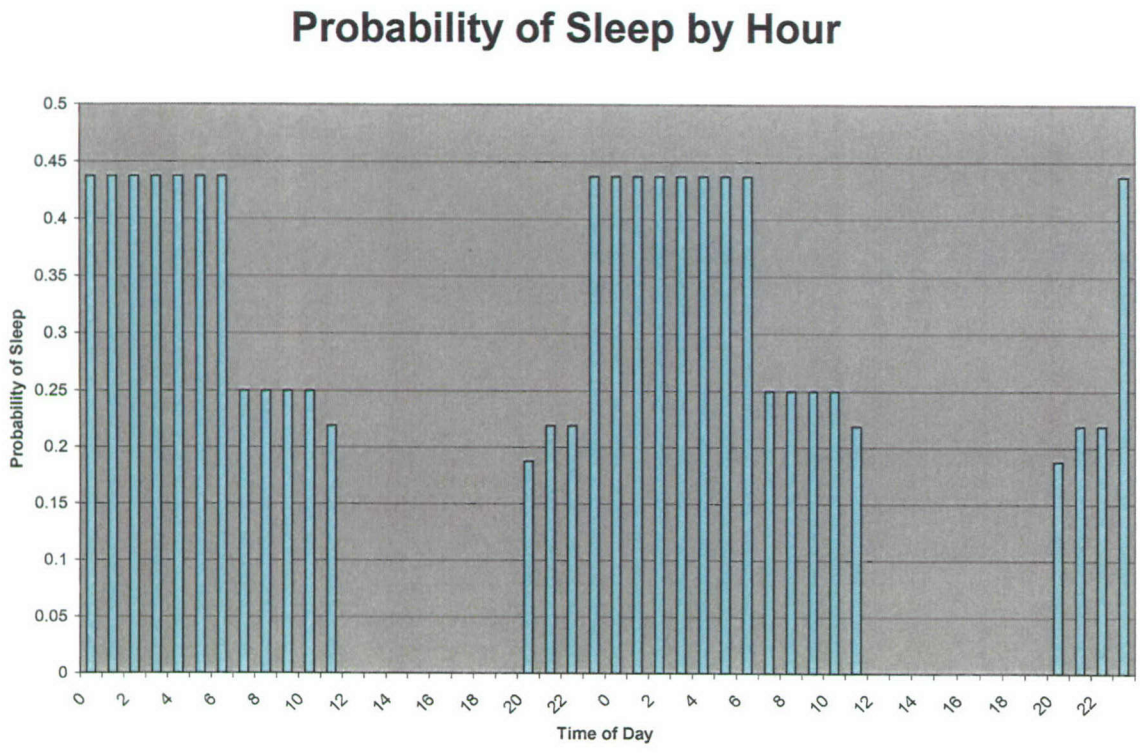

Figure 24. This chart assumes a random distribution of work end hours and a 16 hr break. This chart compares favorably with the earlier observation data (Figure 23).

Auto Sleep User Interface. With a FAST™ schedule open, clicking the Auto Sleep button inserts sleep periods into the schedule on all days that were selected under the Auto Sleep Options screen. The latter is found on the Model drop down from the menu bar. Any sleep already in the schedule on those days will be replaced with that generated by Auto Sleep. Sleep will be automatically scheduled around work periods in the schedule and represents the "normal" habits of a railroad engineer under that work schedule. Those automatic sleep periods may be edited and other sleep periods added to better reflect the specific habits of an individual, unusual working conditions, or to improve performance. If work periods are added to the schedule, Auto Sleep may be selected again to calculate sleep around the new work periods. If no work periods have been entered into the schedule, then all days will be treated as Rest Days and sleep will be entered according to the settings in the Auto Sleep Options screen. See Auto Sleep Options help in the FAST™ Help menu for more details about customizing Auto Sleep to your preferences.

Figure 25 shows the Auto Sleep Options window. The option definitions follow:

- Period for Auto Sleep Calculation – Select whether you want Auto Sleep to apply to the entire period of the schedule (including the 3 days prior to day 0) or to a portion of the schedule. If you select a portion of the schedule, you must specify the first and last day for the period of the calculation.

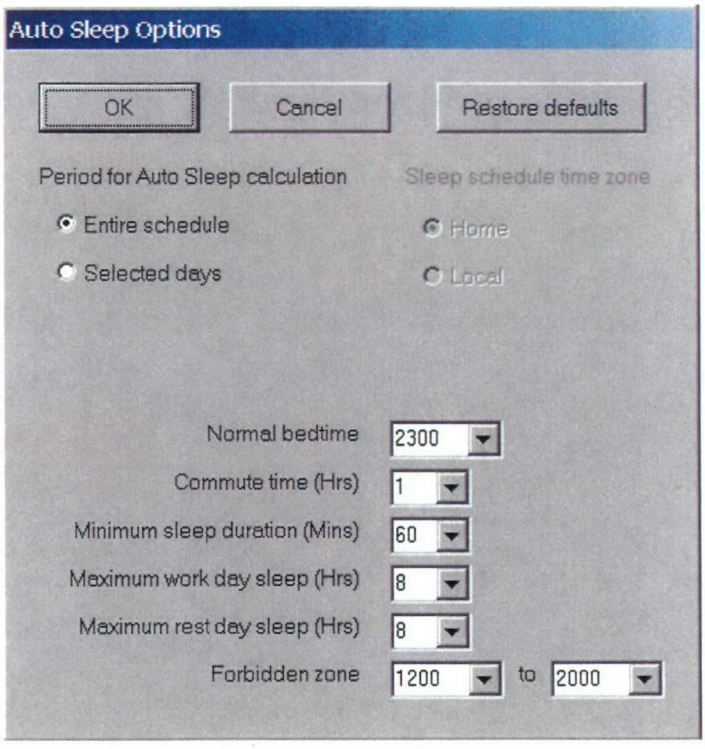

Figure 25. The Auto Sleep Options Screen can be activated by selecting Model and then Auto Sleep Options.

- Sleep schedule time zone – Currently not implemented. The Home time zone is assumed.
- Normal bedtime – The preferred bedtime when not prevented by work.
- Commute time – The number of hours or fractions of hours that are involved in getting to work or back home after work. Include time that is always spent getting ready for work or tending to personal affairs after work. No sleep will be scheduled for this time. For example, if work is 30 minutes away and you spend one hour getting ready to go to work, type 1.5 in this window.
- Minimum sleep duration – The minimum number of minutes that would normally constitute a sleep period. This is the minimum duration for a nap allowed by the Auto Sleep computation.
- Maximum workday sleep – The number of hours that would normally be devoted to sleep on a workday. Auto Sleep will not allocate more than this amount to sleep on any workday.
- Maximum rest day sleep – The number of hours that would normally be devoted to sleep on a non-work day. Auto Sleep will allocate this number of hours to sleep on every rest day. Select a number that represents your average amount of sleep on a rest day, normally not more than 8 to 8.5 hours.
- Forbidden zone – If not working during the afternoon, most railroad engineers do personal business and do not sleep. This period is adjustable. No sleep will be scheduled during this period on any day when work ends prior to noon. Sleep is delayed to start in the evening after the forbidden zone. If the beginning and end of the zone are the same hour, then the forbidden zone is ignored.

Once selections in this list are completed, click OK to save these settings. Auto Sleep will not execute until you click Auto Sleep on the tool bar. The selections that are made will be

automatically saved and will be in effect each time FAST™ is opened. You may restore the program defaults at anytime by clicking Restore defaults. Cancel will exit this screen without saving your changes.

Validation of Auto Sleep
Five independently selected logs from the Pollard (1996) study were evaluated. The work and sleep schedules as recorded in the logs were entered into FAST™ ™. The work schedule was then used to create an Auto Sleep pattern and saved as a comparison file.
The predictions of sleep and effectiveness using Auto Sleep were compared to the same measures based on the actual logs.

General Findings.

- Three of the five logs showed regular patterns of work and sleep.
- One log file (Log 93) showed average amounts of sleep that exceeded 9 hours per day and often zero time to commute from work to sleep.
- One log file (Log 103) showed three days with no sleep followed by a day with nearly continuous sleep.
- All logs were evaluated but only three logs (Logs 101, 102, and 104) were used to evaluate the default settings of FAST™ ™.

Figures 26 and 27 compare Auto Sleep predictions with the actual sleep record logs.

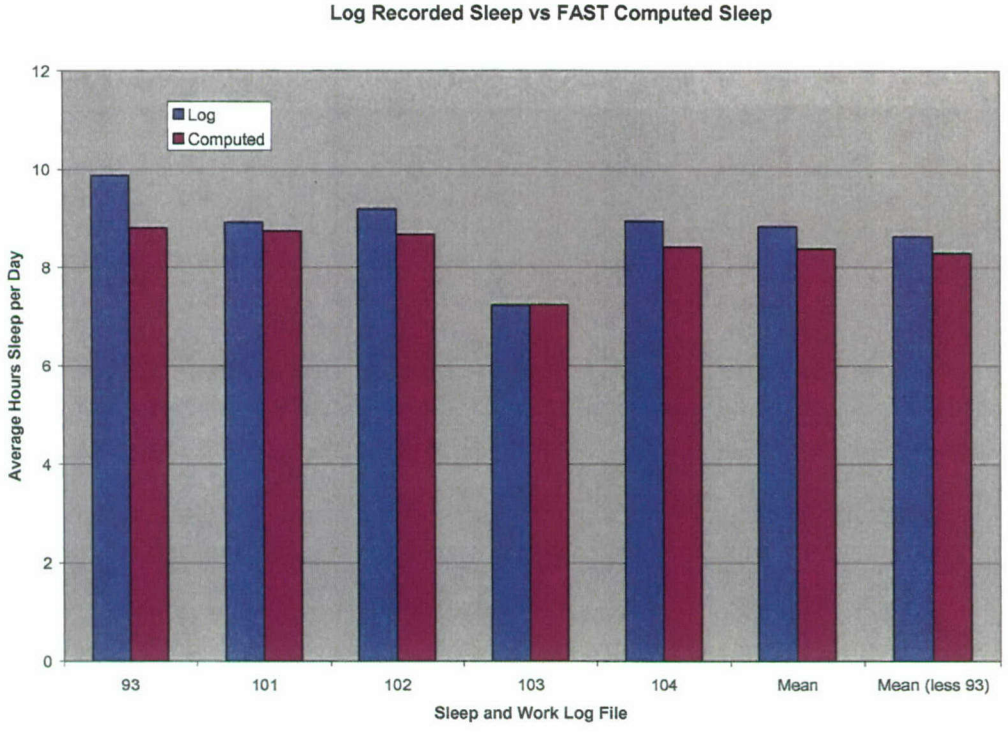

Figure 26. A comparison of Auto Sleep computations with actual sleep logs (all logs).

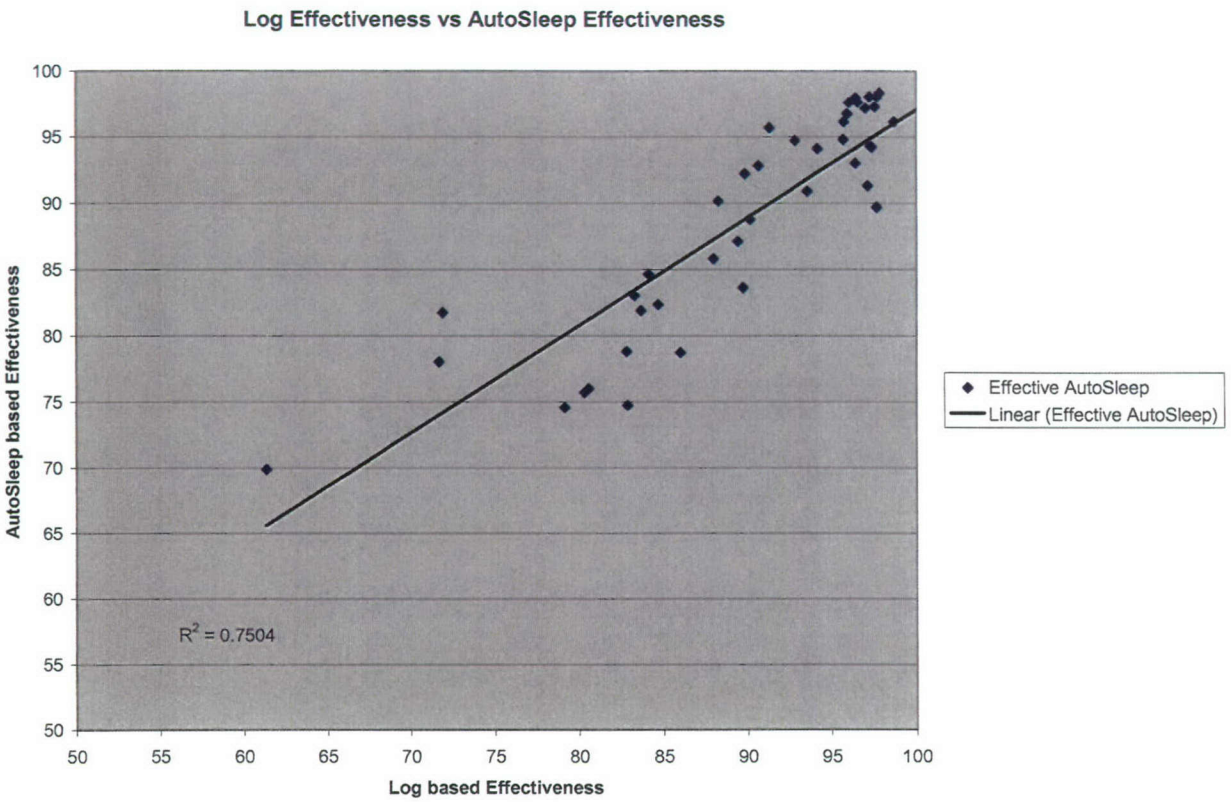

Figure 27. A scatter plot of FAST™ effectiveness predicted by actual logged sleep and Auto Sleep projections.

Conclusions. Auto Sleep makes reasonable predictions of sleep when the pattern of sleep has a regular relationship to work (an average $R^2 = 0.91$ for logs 101, 102, and 104). Idiosyncratic gaps in sleep that are not required by the work schedule are not predicted (Log 103) and unusually long sleep periods significantly longer than 8 hours per day are not predicted (Log 93). Auto Sleep will underestimate effectiveness on days when an extra evening nap is taken in anticipation of a late evening work call. An optional "napping rule" can be implemented in the future to solve this problem. Auto Sleep should be compared to a larger independent sample of logs to fully validate the algorithm. If the user only knows the work intervals of an individual, then Auto Sleep may be used to automatically calculate a reasonable sleep schedule for a person under a specific work schedule that does not involve time zone changes. The Auto Sleep algorithm is consistent with the findings of Foret and Lantin (1972), who also worked with train engineers working irregular schedules.

Subtask 2.5. User Testing of FAST™

Since the end of the FAST™ Phase 1 contract, the FAST™ team has attempted to provide interim copies of the FAST™ software to AF and other interested DoD parties for evaluation and recommendations. To date the AF has a list of 107 persons and organizations that have received free copies of FAST™ to evaluate for their purposes. These evaluations ranged from learning

about what the software could do to actually using it to plan AF military aviation missions. Other uses included evaluating past aviation schedules to confirm subjective impressions of fatigue, evaluating the tool for integration with current or future aviation operations and planning, fatigue factors in accident investigations, deciding among alternative flight schedules for an operation, and scheduling shift work.

The AFRL/HEPF, the Warfighter Fatigue Countermeasures Branch, maintains the database of users in a spreadsheet with the following categories:

- Date Sent
- FAST™ Version
- Name of the individual
- Phone Number
- Organization or Company
- Email address
- Street Address

An abbreviated listing of the AF users and those receiving FAST™ from the AF is included in Appendix 2. To protect privacy, the listing does not include any names or Email addresses, only organizations and their phone numbers. Where only a name or Email address was posted to the database, the entire entry was omitted.

This group of AF users has provided us with excellent information on software problems, new ways to present, manipulate, or input required information, new software features they would like to see added, obstacles in the software the don't integrate well with their scheduling task, and suggestions for improving the software.

In addition, FAST™, version 0.8.16, produced on 11 March, 2002, was evaluated by the Air Force Operational Test and Evaluation Center (AFOTEC) in an Expeditionary Human Performance Enhancement (EHPE) initiative as a part of the Air Expeditionary Force Battlelab (AEFB), (Detachment 1, AFOTEC, 2002). The initiative was designed to provide air expeditionary force commanders and personnel with information to enhance readiness and promote effective fatigue management, particularly during long-duration missions involving multiple time zones. Detachment 1 of AFOTEC, Kirtland Air Force Base, New Mexico, with the assistance of AFRL, Brooks AFB, Texas, performed the EHPE assessment for the AEFB, Mountain Home AFB, Idaho. The project, which commenced in Fall 2000 and concluded in Fall 2002, included assessments of both pharmacological and nonpharmacological interventions for fatigue management. The FAST™ assessment occurred in May/June 2002 in the context of long-duration C-17 airlift missions conducted overseas in support of Operation Enduring Freedom. Three C-17 crews, each consisting of three pilots, deployed from Charleston AFB, South Carolina, to Rhein-Main, Germany (an eastbound flight with a six-hour time advance). Once in Germany, Det 1 AFOTEC continued to collect data from the pilots as they each flew two airlift missions (approximately 20 to 22 hours in duration) into the area of responsibility. The operations tempo of the missions was very rapid, leaving little time for pre-event planning.

The results of their evaluation indicated that:

- FAST™ could not be implemented as planned during the assessment due to the rapidly changing nature of the environment.
- Human Performance Training Team (HPTT) personnel, who would implement FAST™ if it was fielded, suggested that FAST™ may be most useful in helping to identify potential danger zones during a mission when performance effectiveness may drop below 75 percent. However, FAST™ was not used in this capacity during the assessment.
- A six-hour training course covering both fatigue management and the use of FAST™ was not sufficient for expert use of FAST™. Trainees felt they required much more hands-on use of the software for development of realistic schedules.
- Both HPTT scheduler comments and Det 1 AFOTEC's Software Usability Evaluation analysis indicated that FAST™ was too labor intensive and complicated, primarily because of the cumbersome data entry process.
- FAST™ proved to be a relatively poor predictor of PVT performance during this assessment, predicting approximately 34 percent of pilots' PVT scores. FAST™ predictions were more highly correlated with crewmembers' subjective perceptions of sleepiness than with their actual performance data.

On the last point, the PVT task was not administered in a quiet, uninterrupted testing environment required for reliable results. Further, during the FAST™ field assessment, effectiveness and suitability of FAST™ from the perspective of aircrew members who would be using the schedules could not be fully evaluated since FAST™ schedules were not implemented as originally planned. The take-away message was that the FAST™ interface for data entry needed improvement.

The chief recommendation for improving FAST™ involved improving the data entry process so that it is less cumbersome and labor intensive. Suggestions included:

- Simplify the process so that fewer keyboard/mouse entries are required (one suggestion is to have the user answer a series of questions, which the program then uses to automatically build the schedule)
- Revise the tabular display for data entry to accommodate entries in either Zulu or base time
- Allow the user to enter either start times and durations or start and end times to build sleep/work schedules
- Provide the ability to copy/paste in the graphical display

Each of these recommendations was implemented in succeeding versions of FAST™ as documented in Part 2 of this report.

During the development of the new interface for irregular schedules, we met with three AMC schedulers who acted as subject matter experts in a task analysis. This effort and its outcome are documented in Part 2 of this report. Additional feedback has come from commercial users of FAST™ documented under Task 6 of this report.

Task 3 Results: Studies of the Effects of Stimulants on Performance

The planned experiment to collect data on the effects of the eugregoric modafinil was not conducted. The fully approved research protocol entitled, "The Relative Efficacy of Single

Operational Doses of Caffeine, Dextroamphetamine, and Modafinil on Measures of Sleepiness and Performance in Sleep-Deprived Volunteers" is included in Appendix 1. Because the protocol was never executed, due to AF priorities, the data from Pigeau, Naitoh, Buguet, McCann, Baranski, Taylor, Thompson, and Mack (1995), who conducted a study of modafinil, dexamphetamine, and placebo, was used for modeling stimulant effects on performance. Their study of 64 hours of sustained mental work collected cognitive performance data from their participants that are useful for modeling the fatigue countermeasure effects of these drugs. The Pigeau, et al. data were used to develop specific parameters for the two fatigue countermeasures modafinil and dextroamphetamine. The modeling of these data provides a first approximation to the stimulant algorithms for SAFTE/FAST™. The development of these algorithms from Pigeau, et al. was discussed under Subtask 1.3, Countermeasures Effects on Performance. The algorithms developed for SAFTE will only be included in FAST™ after they have been validated with additional data from studies such as the one proposed in Appendix 1.

Task 4 Results: Studies of the Effects of Sleep Aids on Performance

The hypnotic zolpidem and the hormone melatonin were compared systematically at two doses each for their effects on daytime sleep, nighttime cognitive performance and mood in an operationally and militarily relevant paradigm. The participants worked all night. Subsequently, an Early Sleep Group slept from 0800-1600 and a Late Sleep Group slept from 1400-2200. The participants worked all night again, and recovery sleep was monitored the following day and night without sleep aids. Measures included polysomnography, simple and complex cognitive task performance, vigilance, subjective reports, salivary melatonin, and vital signs. In this study, neither zolpidem nor melatonin was successful in improving daytime sleep compared to placebo. Participants slept longer under the medicated treatments, but it was not statistically significant.

Given the sleep outcome, it was not surprising that there were no differences among the sleep aid conditions for alertness, mood or performance. In this study, there were no advantages for morning or afternoon sleepers in nighttime alertness, mood or performance. The Foret and Lantin (1972) findings of 3-4 hours of sleep during the day do not appear to hold for sleep deprived people sleeping under ideal conditions. For two consecutive work nights, ideal daytime sleeping conditions appear to provide nearly as much sleep as a sleep aid and without any risk to nighttime performance. In conclusion, after 24 or more hours of sleep deprivation, excellent sleeping conditions appear to provide nearly as much sleep as a sleep aid (zolpidem or melatonin) for maintaining performance. More research is needed to systematically vary the quality of sleep to better approximate the conditions of sleep found in operational units.

This study did provide excellent laboratory data to validate the SAFTE model. Unfortunately, this study provided no beneficial performance effects of sleep aids to model in SAFTE or FAST™. The study was published as an AF technical report under separate cover.

Task 5 Results: Studies of Sleep and Rest Habits in the Pilot Population and Comparison of Schedule Predictions

Searches were made looking for both military reports and in the general aviation literature for any information on the sleep or rest habits of pilots. Our report concluded that there were no

published studies or reports on when pilots sleep or rest for their missions or flights. The full report identifying the methods of search are documented in a report entitled, "Sleep and rest habits of pilots for irregularly scheduled missions" delivered under this contract.

Task 6 Results: Demonstrate the FAST™ system to potential user populations both within and beyond the Air Force

This section documents marketing that the FAST™ team has conducted throughout the Phase 2 contract. To date NOVA has a database of 104 persons and organizations that have received evaluation copies of FAST™ to review for their purposes. Some of these individuals attended the first FAST™ User Forum.

NOVA Scientific maintains a database of users with the following categories:

- Name of the individual
- Organization
- Department
- Contact info
- Job Title
- Phone Number
- Street Address
- Email Address
- Website
- Experience with FAST™
- Usage
- Industry
- Date Sent
- FAST™ Version

The users can be categorized by industry as in Table 5. Clearly most of the users are categorized as government, but many of those are military. The NOVA database and the AF database overlap in the government category.

Table 5. Categories of FAST™ Users

Industry	Total
Academic	8
Airlines	7
Business	3
Communication	1
Consulting	13
Energy	2
Foreign Gov.	1
Gen. Transportation	9
Government	27
Law Enforcement	2
Medical	6
Railroads	24
Research	1
Grand Total	104

Because we had not asked our commercial users permission to list them in this report we have not. However, what is clear from Table 5 is that there is tremendous interest in FAST™ in the commercial sector and NOVA plans to pursue product sales with them. Many of the FAST™ users in the database have provided us with excellent information on software problems, new ways to present, manipulate, or input required information, new software features they would like to see added, obstacles in the interface that don't integrate well with their scheduling task, and suggestions for improving the software. These users along with those from the AF will provide valuable feedback on new versions of the product as we find ways to improve the product and meet their needs.

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APPENDECES

Appendix 1: Research Protocol entitled, "The Relative Efficacy of Single Operational Doses of Caffeine, Dextroamphetamine, and Modafinil on Measures of Sleepiness and Performance in Sleep-Deprived Volunteers" – Task 3
Appendix 2: Listing of AF FAST™ users and those receiving FAST™ from the AF.

Appendix 1 – Research Protocol

1. Title: The Relative Efficacy of Single Operational Doses of Caffeine, Dextroamphetamine, and Modafinil on Measures of Sleepiness and Performance in Sleep-Deprived Volunteers (JON: 7757P903)

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Scope of Medical Monitoring:

The Medical Monitor will appoint a Medical Observer to be available by telephone throughout the experiment. All technicians involved with the study will receive written instructions on the mechanism for responding to urgent and emergent medical conditions. These instructions will include information on the appropriate medical disposition of participants who are injured or become ill while participating in the research protocol. Minor complaints from the participant (i.e., headache, stomach ache) will be treated as per the medical observer's instructions with over-the-counter medications which are stored in the testing facility. In the case of a true emergency, San Antonio Emergency Medical Service (EMS) will be called for acute cardiac life support (ACLS) or trauma support, and transport to definitive medical care. All others with lesser adverse medical outcomes will be transported to an appropriate military or civilian medical facility for evaluation and treatment as directed by the Medical Monitor or Medical Observer. The Medical Monitor overseeing the protocol must be notified of any serious adverse event resulting from the research exposure within 12 hours. All illnesses or injuries occurring in participants while participating in an experiment, but not causally related to the experiment must be brought to the attention of the Medical Monitor within 48 hours.

5. Contractor and Facility

Veridian Engineering Incorporated
P.O. Box 35482
Brooks City Base, TX 78235

Chronobiology and Sleep Laboratory
8248 Chennault Path
Brooks City Base, TX 78235

6. Objective

The general objectives of this protocol are as follows:

1. Determine whether measures of working memory capacity, which have been shown to be important in predicting higher order cognition, are sensitive to the effects of sleep deprivation.
2. Establish whether data obtained from working-memory tests will predict differential individual vulnerability to sleep loss (thus indicating that such tests ultimately might be useful for selecting fatigue-resistant individuals for staffing sustained operations).
3. Demonstrate the relative efficacy of single, operationally-oriented doses of caffeine (300 mg), modafinil (200 mg), and dextroamphetamine (10 mg) for sustaining the alertness, mood, and cognitive performance of sleep deprived volunteers.
4. Evaluate the side-effects profile of each of the alertness-enhancing compounds when administered to sleep-deprived participants.
5. Establish the extent to which each compound differentially affects a standardized measure of alertness (the Repeated Test of Sustained Wakefulness) versus a standardized measure of sleepiness (the Multiple Sleep Latency Test).
6. Provide sleep and cognitive performance data upon which to model the effects of the three medications.

7. Background

Introduction

Military operations on the modern battlefield often involve lengthy duty periods interspersed with limited opportunities for rest and recuperation. Technological advances such as night vision devices have enhanced the night-fighting capabilities of both ground and air troops, making around-the-clock missions a highly feasible component of the modern military strategy. In the aviation arena, the procurement and deployment of the B-2 bomber, which has an un-refueled range of 6,000 nautical miles, has paved the way for nonstop, intercontinental flights in which a 2-man crew remains in the cockpit for up to 44 continuous hours. Because of these and other modern capabilities, long-duration missions are now commonplace. In fact, the Air Force Chief of Staff recently noted that persistent and sustained operations "24 hours a day, seven days a week…" are essential to attaining U.S. victory in today's battlespace (Elliot, 2001). This is consistent with Air Force doctrine which emphasizes the tactical necessity of sustained and overwhelming application of air and space power in modern warfare (Department of the Air Force, 1997).

Despite the requirements for such long-duration missions, the realities of defense budgets and the resulting limitations on force structure make it difficult to adequately staff "24/7" operations. Since 1990, there has been an overall 37.7 percent reduction in military personnel, and the number of active Air Force tactical wings has fallen from 24 to 12 (Congressional Research Service, 2002). Meanwhile, contingency deployments have increased by as much as 400 percent (Correll, 1998). Thus, military capabilities are increasingly strained as understaffed units strive to accomplish more work with fewer resources. The ultimate result has been diminished military combat readiness (Spencer, 2000), in part, because of increased levels of physical and cognitive fatigue.

Nature of fatigue and effects on performance

Although equipment and aircraft can operate for extended periods without adverse effects, humans need periodic sleep for the restoration of both the body and brain (Horne, 1978). Ignoring this fact leads to cognitive impairments, attentional lapses, and slower reaction times that are associated with poor performance (Krueger, 1989). In addition, sustained wakefulness and the resulting cumulative sleep debt predispose personnel to brief and uncontrollable "sleep attacks" or lapses that can occur even during flights (Dinges, 1995). The longer the period of continuous wakefulness, the more likely these episodes become. Naitoh and Kelly (1993) warn that sleep deprivation in extended operations rapidly degrades motivation, impairs attention, decreases short-term memory capacity, introduces carelessness, degrades physical endurance, compromises verbal communication skills, and impairs judgment. Sleep-deprived personnel can be expected to lose approximately 25 percent of their ability to perform useful mental work with each 24-hour period of sleep loss (Belenky et al., 1994). This means that soldiers who are completely deprived of opportunities to obtain restful sleep almost immediately begin to suffer from a host of fatigue-related problems. They can become totally ineffective after approximately 3 days, especially if they are performing complex tasks.

However, the fatigue-related concerns in operational environments are not limited to those resulting from total sleep loss. Laboratory studies have shown that 2-4 hours of daily sleep restriction (an amount commonly seen in

military deployments) significantly degrades both vigilance and cognitive performance (Balkin et al., 2000). Also, it has been determined that simply remaining awake for 18.5 to 21 continuous hours during a single episode (characteristic of the manner in which operational personnel often transition from day to night shift) can lead to basic psychomotor impairment equivalent to what is seen with blood alcohol concentrations of 0.05 to 0.08 percent (Arnedt et al., 2001; Dawson and Reid, 1997). In light of these data, it is not surprising that fatigue-related, Class-A aircraft accidents alone cost the Air Force over $50,000,000.00 annually in personnel, weapon-system, and property losses (Air Force Safety Center, 2002).

Strategies for countering operational fatigue

There are a variety of strategies for countering the impact of fatigue in operational settings (Babkoff and Krueger, 1992). These can generally be categorized as either nonpharmacological or pharmacological. Once it is determined that a specific approach is operationally feasible, its utility depends on the exact strategy that is chosen and the manner in which it is implemented.

Nonpharmacological approaches. These typically include work/rest guidelines, napping, rest breaks, exercise, environmental stimulation, and ensuring the physical fitness of personnel. As noted below, several non-drug techniques should be considered as "first line" fatigue countermeasures as long as their operational feasibility and efficacy have been established.

Emphasizing proper work/rest management is one strategy that the military has rightfully focused upon. However, when the intensity of combat reaches a certain point, it can be difficult to properly control sleep periods, and this can result in severe on-the-job fatigue (Cornum, 1994; Angus, Pigeau, and Heslegrave, 1992). A recent survey of Army pilots revealed that, even during peacetime, 26 percent complained of poor sleep while in the field or on temporary duty compared to only 5 percent complaining of poor sleep while at home (Caldwell et al., 2001).

Strategic naps can help alleviate sleep-deprivation-related performance decrements in situations where naps are feasible (Dinges et al., 1988). However, scheduling naps is not a simple matter in many military settings. Operational constraints can make it impossible to ensure proper control over nap timing (placement of naps at optimal points in the sleep-deprivation period), nap duration (ensuring sufficient sleep time), and nap scheduling (placing naps at appropriate points in the circadian cycle) (Caldwell, 2001). In addition, it can be difficult to establish a restful and isolated environment in which effective naps can occur.

Brief periods of exercise may offer some benefit in situations where full sleep periods and naps are not possible, but this strategy only temporarily reduces the impact of sleep loss (LeDuc et al., 1998; Horne and Reyner, 1995a; and Angus et al., 1992). Also, there is some indication that the short-term benefits of exercise are not sufficiently robust to outweigh alertness decrements which are subsequently produced by a high level of physical activity.

Exposure to environmental stimulation such as cold air or noise is another strategy that has been tried in laboratory studies of driver fatigue. However, research has shown that such measures are virtually ineffective for maintaining alertness at optimal levels (Horne and Reyner, 1995b).

The tactic of countering fatigue by ensuring high levels of physical fitness anecdotally has substantial appeal. Unfortunately, while this strategy effectively sustains physical endurance, it has little impact on the ability to maintain cognitive performance (Angus et al., 1992).

The knowledge of when and how much fatigue will degrade performance can be used to apply countermeasures to neutralize its effects. The Fatigue Avoidance Scheduling Tool (FAST™™) currently under development for AFRL/HEPM by NTI, Inc., estimates performance effectiveness based on day-to-day patterns of sleep and wakefulness. It is based upon a model development by Dr. Steven Hursh built on 20 years of sleep research. The Sleep, Activity, Fatigue and Task Effectiveness (SAFTE) model integrates quantitative information about (1) circadian rhythms in metabolic rate; (2) cognitive performance recovery rates associated with sleep, and cognitive performance decay rates associated with wakefulness; and (3) cognitive performance effects associated with sleep inertia to produce a 3-process model of human cognitive effectiveness. In the model a circadian process influences both cognitive effectiveness and sleep factors related to sleep onset , sleep duration, and sleep depth (Hursh, et. al. 2003). Sleep regulation is dependent upon hours of sleep, hours of wakefulness, current sleep debt, the circadian process and sleep fragmentation (awakenings during a sleep period). Cognitive effectiveness is dependent upon the current balance of the sleep regulation process, the circadian process, and sleep inertia. FAST™™ is a Windows™ program that allows planners and schedulers to quantify the effects of various schedules on human performance (Eddy and Hursh, 2001). It allows work and sleep data entry in graphic and text formats. The data from the proposed study will be used to mathematically model the sleep and performance effects of the three medications. If valid predictions can be made with the data, the parameters will be included in FAST™™ for use when nonpharmacological fatigue countermeasures are not operationally feasible.

A final strategy is that of selecting "fatigue-resistant" personnel for missions that involve continuous and/or sustained operations. Although this is a largely unexplored approach, it does hold substantial promise. It is clear that there are significant inter-subject differences in the response to sleep deprivation. Van Dongen et al. (2002) suggests that "vulnerability to sleep loss" is an individual trait, and Mallis et al. (2002) has shown this trait is fairly stable--subjects who are highly resistant to fatigue-related decrements on one occasion will behave similarly during subsequent tests, even if the tests are separated by a full year. If the individuals who are most and least vulnerable to sleep deprivation can be identified in an *apriori* fashion, it will be possible to improve performance in operational settings by selecting fatigue-resistant personnel for missions involving sustained operations. Engle (2001) reports that measures of individual differences in working memory capacity predict performance in a wide variety of real-world cognitive tasks. In fact, there is growing evidence that working memory capacity is an important component responsible for differences in general fluid intelligence or moment-to-moment cognitive readiness (Engle, 2002; Engle et al. 1999). People who possess high levels of working memory capacity, versus those with lower levels, are better able to control attention, particularly in the face of interference from competing response tendencies and/or other events that would capture attention away from the maintenance of important task goals and procedures (Kane et al. 2001). The most common measures of working memory capacity, operation span and reading span, may be able to predict which subjects will be able to sustain performance at or near well-rested levels despite the cognitive interference invariably produced from the fatigue associated with sleep loss. Thus, such measures hold promise for use as tools to identify personnel who are particularly well-suited to military sustained operations.

Pharmacological countermeasures. Although the search for non-drug countermeasures for operational fatigue continues, stimulants (or alertness-enhancing compounds) at present remain the most reliable method for maintaining the performance of personnel who are deprived of adequate sleep opportunities. Stimulants are effective and easy to use, and their feasibility is not dependent upon environmental manipulations or scheduling modifications. This explains why pharmacological compounds such as amphetamines have been used extensively in several military conflicts (Cornum, Caldwell, and Cornum, 1997). At present, there are essentially three choices that deserve serious consideration—caffeine, modafinil, and dextroamphetamine.

Caffeine is easy to acquire and socially acceptable, and it appears suitable for sustaining alertness in relatively short (i.e., 37 hour) rather than long (i.e., 64 hour) periods of continuous wakefulness (Lagarde and Batejat, 1995). Caffeine is considered by some to be preferable to amphetamine for promoting alertness in sleep-deprived individuals, but others have concluded that caffeine is less effective than amphetamine and more prone to produce unwanted side effects (Weiss and Laties, 1967). The effectiveness of caffeine may be less than optimal in individuals who normally consume moderate to high amounts in coffee, soft drinks, nutritional supplements, and/or food products, but this has not been firmly established. However, it is known that tolerance to the sleep-disrupting effects of caffeine can occur in as little as 7 days in individuals given high doses (1200 mgs per day), and although the majority of adults consume far less than 1200 mgs per day, it is estimated that about 80 percent of the U.S. adult population regularly consumes a behaviorally active dose of caffeine on a daily basis (Griffiths and Mumford, 1995). However, all of this not withstanding, it has been established that caffeine generally will significantly improve the performance of sleep-deprived people who do not normally consume high doses of this compound. An overview of the existing literature suggests that a single dose of 300 mg may produce alertness-enhancing benefits similar to the Air Force's currently-approved 10-mg of dextroamphetamine, but this has not been experimentally established via prior research efforts. (There have been studies in which 300-mg caffeine doses have been tested and other studies in which 10-mg amphetamine doses have been tested, but there have been no controlled dosage-equivalence studies).

Modafinil is a new alertness-enhancing compound that also is proving efficacious for sustaining performance in prolonged periods of total sleep loss (Lagarde and Batejat, 1995). This substance only recently became available in the United States (it was FDA approved for the treatment of excessive daytime sleepiness in patients with narcolepsy in December, 1998). Testing in militarily-relevant contexts is at this point, insufficient. The one aviator performance study that exists (with 600 mg modafinil given in three divided 200 mg doses) was conducted by the principal investigator of the present protocol. It indicates modafinil is capable of sustaining simulator flight performance at near-rested levels despite over 30 hours of sleep loss (Caldwell et al., 2000); however, there were anecdotal reports that modafinil was associated with side effects such as nausea, vertigo, and dizziness. Studies focusing on ground-based performance have produced more promising results. Lagarde et al. (1995) and Lagarde and Batejat (1995) found that modafinil reduced the frequency of involuntary sleep lapses and maintained cognitive performance during 60 continuous hours of wakefulness, and Pigeau et al. (1995) reported that modafinil (300 mg) was as effective as dextroamphetamine (20 mg) for maintaining mood, alertness, and performance throughout 64 hours of sleep deprivation. Eddy et al. (2001) found that modafinil eliminated fatigue-related performance decrements on a vigilance task in people kept awake for 22 hours. It did so without creating vestibular disturbances.

Wesensten et al. (2002) indicated that modafinil (200 mg and 400 mg) restored response speed and throughput which had degraded after 41.5 hours without sleep. A review of the currently available literature suggests that a single 200-mg dose of modafinil should sustain alertness as well as a 10-mg dose of dextroamphetamine.

Amphetamines have long been known to maintain the performance of sleep-deprived people at or near nondeprived levels (Cornum, Caldwell, and Cornum, 1997). The Air Force authorized the use of amphetamines to sustain the performance of sleep-deprived pilots as early as 1961, and dextroamphetamine continues to be authorized under Air Force policy for certain situations today (10 mg doses). In the laboratory, single doses (20 mg) of dextroamphetamine have been shown to return alertness and cognitive performance to near baseline levels and maintain this recovery for 7 to 12 hours even after 48 hours of total sleep deprivation (Newhouse et al., 1989). In addition, a single 20 mg dose has been found to temporarily prevent performance decrements in subjects kept awake for approximately 34 hours (Pigeau et al., 1995). Studies previously conducted by the principal investigator in this protocol have established that multiple 10-mg doses of dextroamphetamine, administered prophylactically, are able to sustain the performance of helicopter pilots throughout 40 hours of continuous wakefulness (Caldwell et al., 1995; Caldwell, Caldwell, and Crowley, 1996; Caldwell and Caldwell, 1997). A recently completed study (also conducted by the present investigator) extended these results by showing that dextroamphetamine continues to work well in pilots deprived of sleep for up to 64 hours (Caldwell et al., 1999). In these studies, unwanted side effects were minimal (most often consisting of increased blood pressure rather than psychological or cognitive disturbances) and of little or no consequence in healthy young adults. In addition, the preponderance of research indicates no increases in risk-taking behaviors or overestimation of performance capabilities associated with dextroamphetamine—findings which have been confirmed elsewhere (Higgins et al., 1975; Baranski and Pigeau, 1997). The existing data, and approved Air Force policy, indicates that 10-mg doses of amphetamine provide operationally-relevant resistance to the effects of sleep deprivation in aviation contexts.

Summary

Fatigue can be a significant problem in military personnel if not properly addressed. Several potential fatigue countermeasures are available, and while non-pharmacological approaches always should be the "first line" approach, a host of operational constraints frequently limit the usefulness of these types of interventions.

The apriori selection of fatigue-resistant personnel holds substantial promise for properly staffing prolonged missions devoid of adequate sleep opportunities because it is known that some individuals possess a greater capacity to endure sleep loss than others. If a metric for predicting these fatigue-resistant individuals can be discovered, a selection-based approach can be realized. Measures of working memory may permit such predictions, thus allowing determinations about which people are best suited for sustained operations. However, further research in this area is needed.

In the meantime, pharmacological strategies represent the only realistic strategy for maintaining the performance of the majority of operational personnel (regardless of individual differences) in cases where adequate sleep is simply impossible to obtain despite everyone's efforts to the contrary. Although a great deal is known about the effects of caffeine, modafinil, and dextroamphetamine, the choice of which compound is best for specific military applications remains unclear. Despite years of research on these three substances, a search of the scientific literature indicates there has not been a single study in which a direct, placebo-controlled comparison of typical operational doses of caffeine, modafinil, and dextroamphetamine has been conducted. Thus, it is difficult to determine with any degree of certainty 1) the relative efficacy of a single dose of each drug for sustaining the basic physiological alertness and cognitive performance of sleep-deprived subjects, 2) the relative onset and duration of action of each medication, 3) the relative side-effect profile of each compound, and 4) the relative impact on "sleepiness" versus "alertness." It has been noted that caffeine (300 mg) and modafinil (200 mg) will not completely prevent the onset of sleep in sleep-conducive conditions (Kelly, Mitler, and Bonnet, 1997; Lagarde et al., 1995); whereas dextroamphetamine (10 and 20 mg) will (Newhouse et al., 1992). Such a difference can have significant operational ramifications in terms of how and when each of these countermeasures can best be employed. For instance, if it is true that caffeine and modafinil can promote alertness when needed without compromising the ability to gain opportunistic sleep (via a short nap), perhaps these compounds would be ideal for operations in which unscheduled napping episodes are expected to become available, but in which personnel otherwise will be fully engaged in active work tasks. If dextroamphetamine produces such a high degree of stimulation that sleep becomes impossible even in the most soporific settings, perhaps this is the drug of choice in operations that consist largely of monotonous tasks that nonetheless require long periods of continuous vigilance.

8. Impact

This study will potentially identify a metric for selecting fatigue-resistant individuals for staffing continuous and sustained operations in which opportunities for sleep are extremely limited or nonexistent. This will be done by examining the degree to which the results of working-memory tests (the proposed metric) coincide with decrements on tests that have been more typically used in sleep-deprivation paradigms). In addition, this study will identify the most optimal pharmacological countermeasure for preventing performance and alertness decrements in military personnel who are unavoidably deprived of adequate sleep in operational settings. This study may indicate that different pharmacological compounds should be utilized depending on the unique characteristics of specific military contexts. The study will provide sleep and cognitive performance data upon which to model the effects of the three medications.

9. Experimental Plan

a. Equipment and Facilities

This study will utilize the Chronobiology and Sleep Laboratory (CASL) in Bldg. 1192. CASL contains an array of assessment tools many of which will be used here and are described below.

b. Participants

Sixteen **to twenty** participants, between the ages of 18 and 45 will be recruited from the Brooks City-Base/San Antonio, TX, area. These active-duty and non-active-duty military participants will be representative of the military population (see AFI 48-123, Attachment 2, standards). Female participants will be used if available. Power calculations, using a medium effect size, an alpha level of 0.05, and a power of 0.80, indicate that 16 participants is an adequate number for this design. These volunteers will be solicited via recruitment notices announced in newspapers and posted in various locations as well as via an information brief to be distributed to unit commanders (see Appendices F and G). If any of the primary sample of 16 subjects fails to complete the protocol, he/she will be replaced so that the final data set will consist of a full complement of 16 volunteers. In addition to the 16 main participants, two pilot participants will be subjected to an abbreviated schedule before the actual study begins in order to assess the timing of the tests and procedures. These two participants will not receive any active medication during their participation, and their data will not be included in the final analysis. Slight adjustments to the testing schedule times (no more than 30 minutes) may be made if problems occur during the pilot tests. All potential participants, including the pilot participants, will be given a full explanation of all procedures involved in participation and must sign the informed consent agreement (see Appendix E). Each potential participant will meet one on one with the principal investigator or his representative before enrollment in the study. The study procedures will be explained, the informed consent will be presented for review, and opportunities to ask questions will be given. Potential participants will be screened for current significant medical problems (including sleep abnormalities), current use of medications (other than oral contraceptives, sodium naproxen, ibuprofen, acetaminophen, aspirin, or other medication that will not alter CNS functioning) that cannot be discontinued, difficulty swallowing food substances and/or pills, use of nicotine, or excessive use of caffeine (no more than three 8-ounce cups caffeinated coffee or five 12-ounce caffeinated soft drinks per day). Once all questions are addressed and the potential participant signs the informed consent, he/she will meet with the study physician. Medical records will be reviewed and a brief one-on-one interview will be conducted by the physician prior to testing to determine whether the person is fit to participate in the study (see Appendix C). Participants will be instructed to abstain from drug and alcohol use for 48 hours prior to the beginning of the study, and no drug, alcohol, or caffeine use (other than the study dose) will be permitted during participation. Participants will be tested either alone or in groups of two. (Each participant will have his/her own private test area, bedroom, and bath in the testing facility). Volunteers will remain inside the laboratory at Brooks City Base, TX, for the duration of each of the four phases (drug 1, drug 2, drug 3, placebo) of the study (three consecutive days and two nights). They will return home between test phases to resume their normal activities. Each volunteer will be paid for participating in this effort. The study will require a total of 205 hours of time per individual (61 hours for the first test period, and 48 hours for the following 3 test periods). Participants will be paid a total of $3075.00 ($15.00/hr). Both males and females will be used as available. Participants will be normally entrained individuals (i.e. no night-shift workers). A urine-based pregnancy test will be performed on all female volunteers to ensure they are not pregnant. Pregnancy testing will be conducted by CASL personnel within 48 hours prior to each dose-administration period using a CLIA-exempt test kit provided by the Brooks clinic or an FDA-approved, over-the-counter, home pregnancy test kit. The CASL research staff will have been trained and certified by the Brooks Clinic, laboratory personnel and will follow the certified testing procedures.

c. Duration of Study

Each participant will experience one experimental period per week (three days per period) for four successive weeks. The first experimental period will be longer than the remaining periods since training sessions for the cognitive tests will begin the morning of the first day. The remaining experimental periods will begin the evening of the first day. If for some reason it is not possible to test a volunteer on successive weeks, a maximum of 3 weeks separation between any 2 experimental periods will be permitted; however, every attempt will be made to avoid such an occurrence.

d. Description of Study

Experimental Design. This study uses a two-factor, repeated-measures design with four levels of the drug factor (dextroamphetamine, modafinil, caffeine, or placebo), and nine levels of the session factor (two baseline sessions and seven post-drug sessions) for all tests except the PVT and FIT. For these tests, a total of 4 baseline sessions and 14 post-drug sessions will be analyzed. Each participant will experience all conditions. Experimental sessions will be separated by no fewer than 2 days and no more than 14 days. Presentation order of the conditions will be balanced by a Latin square design. A layout of the design is given in Appendix A.

Data Collection. Data will be acquired with double-blinding. The data collection methods have been selected to assess the major facets of human performance which would impact sustained or night military operations. Cognitive and vigilance performance, mood, and sleepiness will be examined. Prior to the start of data collection, an 8-hour orientation and training period will be conducted to introduce the participants to the purpose of the study and the data collection procedures. During the orientation participants will be trained to asymptotic performance on each of the cognitive performance measures. Each participant will perform two times those tests for which training is not an issue. The order of testing for each task is presented in Appendix B, along with the time of each task. Each participant will be assigned a randomized participant number under which their data will be recorded so as to maintain anonymity.

- *Mood evaluation* – The Profile of Mood States (POMS) (McNair, Lorr, and Droppleman, 1981) will be used to assess subjective reports of mood at various times throughout the test sessions. This paper-and-pencil questionnaire consists of 65 items which measure affect on 6 scales: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. The original questionnaire has been programmed for computer administration and scoring.
- *Sleepiness/alertness evaluations* – Subjective sleepiness will be measured via a variety of procedures listed below:
    - The Visual Analogue Scale (VAS) consists of eight 100 mm lines centered over the adjectives 'alert/able to concentrate', 'anxious', 'energetic', 'feel confident', 'irritable', 'jittery/nervous', 'sleepy', and 'talkative' (Penetar et al., 1993). At the extremes of each line, 'not at all' and 'extremely' will be printed respectively. Scores consist of the distance of the participant's mark from the left end of the line (in mm). This questionnaire will be presented on a computer screen and scored by computer program.
    - Objective measures of alertness will be obtained using the Repeated Test of Sustained Wakefulness (RTSW) (Hartse, Roth, and Zorick, 1982) in which the participant's electroencephalogram (EEG) will be recorded for up to 20 minutes using a Notta polysomnographic system. The EEG signal will be digitized at 200 samples/sec, monitored in real time as well as stored on computer during the test to objectively determine whether or not the participant successfully remains awake. The EEG data from electrodes C_3, C_4, O_1, and O_2, referenced to contralateral mastoids (A_1 or A_2) will be recorded. Eye movements (EOG) will be assessed with electrodes affixed to the outer canthus of each eye and referenced to A_1. Muscle activity (EMG) will be recorded from submental electrodes affixed with adhesive collars. The time constant for the EEG channels will be 0.3 seconds, and the high filter will be 35 Hz. For EOG, the time constant will be 5.0 seconds, and the high filter will be 10 Hz. For EMG, the time constant will be 0.003 seconds, and the high filter will be 120 Hz. The 60 Hz notch filter will be used as necessary. Participants will be required to lie on a bed in a quiet, darkened room after being instructed as follows: "lie as still as possible with your eyes closed and do your best to remain awake." They will be awakened and removed from the room immediately if they fall asleep. If they do not fall asleep after 20 minutes, participants will be removed from the room.

Records will be scored visually in terms of the number of minutes from lights out until the first indication of stage 2 sleep (up to 20 minutes).

- Objective measures of sleepiness will be obtained using the Multiple Sleep Latency Test (MSLT) (Carskadon et al., 1986). Identical measurements will be recorded as is done during the RTSW, with the only difference being the instructions given prior to each test. Participants will be required to lie on a bed in a quiet, darkened room after being instructed as follows: "lie as still as possible with your eyes closed and try to fall asleep." Participants will be awakened and removed from the room if they fall asleep as indicated by the first indication of stage 2 sleep (up to 20 minutes) or, if they do not fall asleep after 20 minutes, they will be removed from the room. Records will be scored visually in terms of the number of minutes from lights out until the first indication of stage 2 sleep (up to 20 minutes).

- *Cognitive evaluations* – Several cognitive tests will be administered to measure a variety of mental processes. The measures from these tests will provide data for modeling the performance effects of the medications as well as test hypotheses. The tests are listed below:
  - The Multi-Attribute Test Battery (MATB) is a computerized aviation simulation test requiring participants to perform an unstable tracking task while concurrently monitoring warning lights and dials, responding to auditory requests to adjust radio frequencies, and managing simulated fuel flow rates. This computerized test is controlled by a Pentium computer equipped with a standard keyboard, a joystick, and a mouse. Data on tracking errors, response times, time-outs, false alarms, and accuracy rates will be calculated automatically by computer.
  - Vigilance performance will be assessed using the Psychomotor Vigilance Task (PVT), a portable simple reaction time test known to be sensitive to sleep loss (Dinges et al., 1997). The PVT requires sustained attention and discrete motor responses. The 8" x 4.5" x 2.4" portable, battery-operated device visually displays numbers counted up by milliseconds in a window. The stimulus is presented for up to 1 minute (60,000 msec), allowing the participant to respond. The participant presses a microswitch which allows reaction time to the stimulus to be recorded. The interstimulus interval varies randomly from 2 to 12 seconds. The data are stored on computer and reduced by custom software for future analysis. Training requires only one 10-minute practice session.
  - The Automated Neuropsychological Assessment Metrics (ANAM) neurocognitive battery (Reeves et al., 1993) will be similar to batteries we have used in the past to monitor fatigue. The entire group of tests will last approximately 14 minutes and will include tests of:
    - *Grammatical Reasoning* – The logical reasoning – symbolic is an adaptation of the task developed by Baddeley (1968). It is a linguistic task requiring knowledge of English grammar and syntax. It also requires the ability to determine whether various simple sentences correctly describe the relational order of two symbols. This implementation differs from the original paper and pencil version in that stimulus pairs are presented one at a time and are screen-centered rather than left-justified to reduce differences in visual search times. On each trial the symbol pair "# &" or "& #" is displayed along with a statement that correctly or incorrectly describes the order of the letters as depicted in the example: "&#" "# is first" The participant decides as quickly as possible whether the statement is true or false and then presses the corresponding response button.
    - *Mathematical Processing* – During the Mathematical Processing task, arithmetic problems are presented in the middle of the screen. The task involves deducing an answer and then deciding if the answer is greater-than or less-than the number five. Each problem includes two mathematical operations (addition and/or subtraction) on sets of three single-digit numbers (e.g., 5 + 3 - 4 = ?). The participant is instructed to read and calculate from left to right and indicate whether the answer is greater-than or less-than five by pressing one of two specified response buttons. The operators and operandi are selected at random with the following restrictions: only the digits 1 through 9 are used; the correct answer may be any number from 1 to 9 except 5; greater-than and less-than stimuli are equally probable; cumulative intermediate totals have a positive value; working left to right the same digit cannot appear twice in the same problem unless it is preceded by the same operator on each occasion (e.g., +3 and +3 are acceptable, while +3 and -3 are not); the sum of the absolute value of the digits in a problem must be greater than 5.

- *Simple Reaction Time* – This test is almost a pure reaction time test which does not include a vigilance portion as does the PVT. Participants watch a computer monitor where a stimulus is presented in the middle of the screen. The participant responds as by pressing the left mouse button quickly as possible. The interstimulus interval varies from 1 to 4 seconds, with a total of 20 presentations of the stimulus. Reaction time is calculated and stored by computer.
- *Spatial Processing Ability* – During the spatial processing (simultaneous and successive) test, pairs of four-bar histograms are presented either simultaneously or successively on the monitor. The histograms are presented as pairs and the participant is requested to determine whether they are identical. One histogram is always rotated either 90 or 270 degrees with respect to the other histogram. The participant responds by pressing a specified key or mouse button to indicate that the two histograms are either the "SAME" or "DIFFERENT."
- *Running Memory (N- back)* – Running memory is a continuous number comparison task (Stanny, 1994). In the running-memory task, subjects are asked to monitor a randomized sequence of numbers, 0 through 9. The numbers are presented one at a time in the center of the screen. Subjects are asked to continuously monitor the numbers and press a specified key or button if the number on the screen matches the number that immediately preceded it. They are requested to press a different specified response button or key if the number doesn't match the immediately preceding number. Running memory is one of ANAM's most sensitive tests. It is similar in format to Gronwall's Paced Auditory Serial Addition Test in that it is forced paced and requires continuous high-level updating of working memory. It is primarily a sustained attention/concentration task.

- Working memory capacity (WMC) will be assessed using the Automated Operation Span (AOSPAN) task, an automated version of the operation span task developed by Turner and Engle (1989). The original OSPAN has been tested for nearly 20 years and has repeatedly been shown to be a valid and reliable instrument for WMC. However, OSPAN is cumbersome to use in a real-world testing situation and requires the full-time attention of the tester. Therefore, Dr. Engle developed the AOSPAN, which is an automated version of the operation span task. This task consists of participants being presented with arithmetic string equations and responding as to whether the equation is correct or incorrect. For example, "Is 8/2 + 1 = 3"? After each string, the participant sees one of 12 letters for about one second. After a series of 2-7 of these arithmetic strings and letters, the participant is asked to recall the letters in correct order. They see a matrix of the 12 letters and a line at the bottom of the screen. They click on the letters individually to build their response string on the bottom line and then they click to finalize their response. They see three sets of each series length. The number of letters from perfectly recalled trials is the AOSPAN score. This score has been shown to have reasonable correlation with other versions of the OSPAN and one sample of 103 participants showed a correlation between AOSPAN and the Ravens Advanced Progressive Matrices task of 0.52. This is on the order of the same correlation as between other working memory capacity tasks and the Ravens.
- The FIT Workplace Safety Screening Evaluation 2500 (PMI, Inc.) pupillography system will be used to record saccadic eye movements and pupil responses to help estimate levels of physiological arousal. The FIT is a computerized fitness-for-duty test which requires subjects to peer into a device in which visual stimuli (both moving and stationary) are presented. The device detects changes in pupil size (as small as 0.05 mm) and movements of the eye (as small as one degree) in response to controlled flashes of light and moving light targets. Measures of saccadic velocity, pupil diameter, pupil-contraction latency, and pupil-constriction amplitude are integrated into a weighted "fitness index" which purportedly is sensitive to the effects of fatigue, stress, and drugs (PMI, Inc., 1999).

- *Grip Strength* –Grip strength will be assessed with a hand dynamometer. Each participant will be placed in a chair and will then be given a brief introduction to the hand dynamometer and its use and proper positioning. The dynamometer will be placed in the participant's dominant hand and the participant will be told to squeeze as hard as they can. Each participant will squeeze three times with their dominant hand and will be given a 1-minute rest between trials. All three scores will be recorded for subsequent analysis.

- *Polysomnography* – Evaluations of sleep architecture during the initial sleep period will be made using a Notta polysomnographic system. The EEG data from electrodes C_3, C_4, O_1, and O_2, referenced to contralateral mastoids (A_1 or A_2) will be recorded. Eye movements (EOG) will be assessed with electrodes affixed to the outer canthus of each eye and referenced to A1. Muscle activity (EMG) will be recorded from submental electrodes affixed with adhesive collars. Data will be collected at a sampling rate of 200 hz. The time constant for the EEG channels will be 0.3 seconds, and the high filter will be 35 Hz. For EOG, the time constant will be 5.0 seconds, and the high filter will be 10 Hz. For EMG, the time constant will be 0.003 seconds, and the high filter will be 120 Hz. The 60 Hz notch filter will be used as necessary. Sleep stages will be scored by standard procedures (Rechtschaffen and Kales, 1968) in 30-second epochs. Data will be reduced to minutes in each stage of sleep (stages 1, 2, 3, 4, and Rapid Eye Movement (REM)), minutes to sleep onset (first full minute of stage 2 sleep), minutes in movement time, latency to the first REM period, total sleep time, and sleep efficiency.
- *Questionnaires* – At the end of each experimental session, participants will be given a Stimulant Effects Questionnaire (Appendix D) in order to determine if adverse effects occur after the administration of each stimulant.

Pharmaceutical Management and Dosing. Facilities at Brooks AFB have been fully approved for the storage and maintenance of Class II-V pharmaceuticals by the Drug Enforcement Agency. Controlled drugs will be handled in accordance with AFRL/HEP 01 44-102, "Research Drug Control." Drug packaging and blinding will be prepared by the pharmacy staff at Wilford Hall prior to the beginning of the study.

Each participant will be exposed to both the active medication and the placebo in a counter-balanced fashion. Participants will be randomly assigned to receive a dose during each test period, one dose per test period, balanced in a Latin square design. Drug administration will be double-blind. Each dose of medication will be placed in gel, psyllium-filled capsules containing either 10 mg dextroamphetamine, 200 mg modafinil, 300 mg caffeine, or placebo. Placebo capsules will be filled with Metamucil®, a psyllium fiber. The participant will be given two capsules at each dose because this will ensure that the capsules are small enough to be easily swallowed (a capsule with sufficient capacity to contain two 5-mg dextroamphetamine tablets or a single 200-mg modafinil tablet would be uncomfortably large for some volunteers). For the dextroamphetamine condition, both capsules will contain 5 mg dextroamphetamine. For the modafinil condition, one capsule will contain 200 mg modafinil and one will contain only psyllium. For the caffeine condition, one capsule will contain 200 mg caffeine and one will contain 100 mg caffeine. For the placebo condition, both capsules will contain only psyllium. Doses will be administered at 2355 with 8 ounces of water.

It is clear that the pharmacokinetic properties of caffeine (specifically "time-to-peak-plasma-concentration" and "elimination half-life") are different from those of dextroamphetamine and modafinil (the pharmacokinetics of these latter two compounds are more similar). However, no attempt will be made to adjust dose-administration times in an effort to ensure that tests are administered under peak drug effects for each compound, because this is quite probably impossible to accomplish in our research facility. Also, it has not been clearly established that peak plasma levels of caffeine, modafinil, and dextroamphetamine necessarily correspond to peak behavioral effects. It is well known that plasma concentrations of drugs do not necessarily correspond to site-of-action concentrations, and that there can be substantial delays from the time to peak plasma concentrations to the time of maximum "site effects" (Greenblatt, 1995). In addition, the approach of staggering dose/test times would be less operationally-useful than the one we have chosen. Although the use of a standard dose time for each substance may show that caffeine's effects generally occur earlier and last for a shorter period of time than modafinil's effects or dextroamphetamine's effects, this would be important data for operational personnel who, based on the findings from this study, will know how long they should wait before the benefits of each of the three compounds should be expected to become evident.

Given that the participants in this investigation will cycle through all of the tests every 3 hours, there should be sufficient testing frequency to ensure that efficacy comparisons can be made—given that there will be significant overlap in the drug-concentration curves. To further ensure accurate tracking of drug effects, one of the tests (the 10-minute PVT) will be used every hour. This strategy is more feasible than a "peak-matching" strategy, especially in light of the fact that the literature indicates substantial inter-individual variance in drug pharmacokinetics, presumably due to individual metabolic/chemical/physical differences. Consider the published information on caffeine: After oral ingestion of caffeine, peak plasma concentrations are estimated to be attained within 1 hour, but they have been observed to occur as early as 15 minutes (Arnaud, 1987). The half-life falls within the range of 3-7 hours, with an average half-life of 4.9 hours (Serafin, 1996; Benet, Oie, and Schwartz, 1996). The rate of caffeine metabolism is significantly higher in smokers than in nonsmokers, producing a shorter half-life in these subjects (Parsons and Neims, 1978). (Smokers will not be included in the pool of participants for this study.) Caffeine's

pharmacokinetics are generally thought to be linear and dose-independent, but Kamimori et al. (Kamimori et al., 1995), recently reported that higher doses of caffeine (150 vs. 300 vs. 600 mg) are metabolized and cleared more slowly than lower doses in sleep-deprived individuals. Similar variability no-doubt exists in the pharmacokinetics of dextroamphetamine and modafinil; however, both of these compounds appear to produce peak plasma levels about an hour later than caffeine, with half-lives that are approximately twice as long. For dextroamphetamine, a single dose of two 5 mg tablets has been shown to produce an average peak blood level of 29.2 ng/ml at approximately 2 hours. The average half-life is 10.25 hours (Physician's Desk Reference, 2001). It has not been determined whether dextroamphetamine is metabolized differently in sleep-deprived versus well-rested subjects. Modafinil is likewise rapidly absorbed and produces peak plasma levels in 2-4 hours (Physician's Desk Reference, 2001; Cephalon, 1998). Cephalon product literature further states that modafinil's half-life ranges from 10-14 hours. The overall half-life after multiple doses has been estimated at 15 hours. There are no data on the extent to which sleep deprivation affects the pharmacokinetic properties of this medication.

Based on these data, it would seem futile to attempt to equate peak concentration curves for the three compounds across the 16 volunteers slated for testing in this investigation. Furthermore, it should be noted that a staggered dosing schedule could be further complicated by circadian-related modifications in drug metabolism. It has been established that the pharmacokinetic properties of several drugs are affected by the time at which they are administered (Lemmer, 1995; Wirz-Justice, 2001). This factor, combined with the individual differences already noted, suggests that a more straightforward, standardized dosing/testing approach will yield the most useful results.

e. Data Analysis

Statistical Analysis: A repeated measures analysis of variance (ANOVA) with two within-subject factors (four drug conditions and nine sessions (two pre and seven post drug)) will be performed on each outcome variable. Within the analysis, polynomial contrasts will be performed to test for a general trend over the time points, and to test whether the trends differ among drug conditions. In addition, if significant drug by time interactions are detected, post-hoc tests will be performed to identify specific drug differences at each time point, separately.

Statistical Power Analysis: All testing will be performed at the 0.05 alpha level. Since the primary goal of this study is to evaluate the effects of three different stimulants on performance, we are most interested in the comparison of the performance changes that occur under the four drug conditions (dextroamphetamine, modafinil, caffeine, and placebo) across time. Consequently, our power analysis is based on the post-hoc comparison (paired t-test) of the change in performance between the two drug conditions within each session, particularly during the mid morning and after times. For these post-hoc comparisons, when testing at the 0.05 alpha level, a sample of 16 subjects will provide an 80% chance (power=0.80) of detecting a difference that is about 0.8 within-subject standard deviations in magnitude (i.e., a standardized effect size of 0.8). We plan to recruit up to 20 subjects so that, taking a drop-out rate into account, we may obtain data from a sample of 16 participants.

f. Expected Results

It is hypothesized that performance will be better and alertness higher during the stimulant conditions than during the placebo condition (one-tailed hypothesis) of at least one standard deviation. The anticipated beginning and duration of performance changes are unknown; however, it is expected that improved performance following dextroamphetamine and modafinil will remain longer than that following caffeine. However, the expected changes between dextroamphetamine and modafinil are unknown.

g. Informed Consent

Each participant will read and sign an approved consent form (Appendix E).

10. Medical Risk Analysis

The data collection procedures utilized in this study are typical of human performance studies and do not increase the risk to participants. With regard to the test compounds, there are potential side effects associated with each of the drugs, but the scientific and clinical literature suggest that the risk of serious or long-term medical complications are virtually nonexistent in healthy young adults. It should be noted that one-time doses of up to 600-mg caffeine (twice the amount to be administered in this study) are widely considered to be safe; and that the FDA has approved dextroamphetamine administrations of up to 60 mg per day (6 times the amount proposed here) and modafinil administrations of up to 400 mg per day (twice the amount to be administered in this investigation). Furthermore, a standard 10-mg dose of dextroamphetamine is currently authorized (in specific aviation contexts) by the U.S. Air Force (message from HQ ACC/DO dated 201406Z Mar 01, ACC Guidance to the Aircrew Fatigue Management Program),

and the operational use of 200-mg doses of modafinil has been recommended (Col P. Demitry, personal communications, Operational Pharmacology Meeting, Falls Church, VA, 2002).

The most common side effects of dextroamphetamine include: palpitations, tachycardia, and elevated blood pressure. The most common adverse CNS reactions are over stimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, tremor, and headache. The most common adverse gastrointestinal reactions are dryness of mouth, unpleasant taste, diarrhea, or constipation. Other adverse reactions can include urticaria, impotence, and/or changes in libido (Physicians' Desk Reference, 2001). The most common side effects of modafinil include: headache, nausea, nervousness, anxiety and insomnia (Cephalon, 1998). Generally, these reactions are mild or moderate. The frequency with which the most common treatment-emergent whole-body, digestive, respiratory, and nervous-system adverse experiences have occurred with daily 200- and 400-mg doses in patient populations was: headache-50%, nausea-13%, rhinitis-11%, and nervousness-8%. Unlike amphetamine, modafinil is not associated with significant cardiovascular stimulation. The most common side effects of caffeine include restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, muscle twitching, rambling flow of thought and speech, rapid heart beats, feelings of inexhaustibility, and/or psychomotor agitation. Most of these symptoms are associated with an excessive amount of caffeine intake (Strain and Griffiths, 1997).

There is no evidence of withdrawal symptoms following discontinuation of one dose of any of these substances. There is little chance that "hangover drug effects" will be problematic for any participant since they will not depart the experimental test facility until 46 hours post-dose. Given the half-life of these medications (dextroamphetamine is 10 hours, modafinil is 12-14 hours, and caffeine is 6 hours, on average), insignificant amounts of the substance (if any) will remain in the participant's system by the end of the data collection period.

Due to the amount of sleep deprivation the participants will experience during each test period (40 hours), each participant will be driven home by a person of their choosing or by other safe means of transportation. He/she will be advised that it is unsafe to drive, operate complex machinery, or engage in other potentially dangerous tasks until he/she has obtained two full nights of sleep over the 48 hours following the test periods.

Risk associated with pregnancy. In 1980, the FDA released a warning statement advising against the use of caffeine during pregnancy, despite a lack of definitive human data on this issue. Animal studies have shown an increased incidence of birth defects when caffeine is administered to rodents in a large bolus, usually 250 mg or more. Such high caffeine doses are typically associated with delayed skeletal ossification, palate malformation, and missing digits. Primate studies have shown an association with spontaneous abortion (SAB), stillbirth, decreased weight gain and low birth weight. Dextroamphetamine also should be avoided during pregnancy. It is a Food and Drug Administration (FDA) Category C compound that, although not studied extensively in pregnant humans, has been shown to have teratogenic effects in animals. Infants born to mothers who were dependent on amphetamines have suffered from low birth weight, and there is evidence the premature deliveries may result. Clinical guidance suggests that Dexedrine should only be administered to pregnant females when the risk/benefit ratio is clearly favorable. Modafinil also should be avoided during pregnancy. Animal studies to assess the effects of modafinil on reproduction and the developing fetus have not been conducted at adequately high doses or according to guidelines which would ensure a comprehensive evaluation of the potential of modafinil to cause embryolethality or teratogenicity. As there have been no adequate or well controlled studies of modafinil in pregnant women, it is contra-indicated for use in pregnancy and lactation.

Minimizing risks associated with pregnancy. Female participants who choose to participate in this study will be required to submit to a urine pregnancy test within 48 hours prior to the planned experimental session. The result must be negative to allow them to participate as there is an undetermined risk of damage to the unborn fetus. Military members may accomplish the pregnancy test at the Brooks or another Air Force laboratory during operating hours. Should clinic testing be impossible, pregnancy testing will commence on the morning prior to each testing session using a test kit exempt from the Clinical Laboratory Improvement Act (CLIA) and provided by the Brooks clinic, or an FDA-approved, over-the-counter home pregnancy test kit. CASL personnel will be trained and certified by the Brooks Clinic, laboratory personnel who will follow the certified testing procedures. Additional precautions against pregnany will be taken by requiring that female participants use contraceptive practices while participating in this study.

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Appendix A
Experimental Design

Test Period One

Time of Day	Day 1 – Training	Day 2 – Training/*Baseline*	Day 3 – Testing
0000			RTSW/Vitals/MSLT PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS
0300			RTSW/Vitals/MSLT PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS
0600 0700		Wake-up	RTSW/Vitals/MSLT PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS
0900	Report to Laboratory Informed Consent Medical Evaluation Electrode Application	ANAM/MATB Working Memory (2 times each) PVT/FIT	RTSW/Vitals/MSLT PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS
1200	ANAM MATB Working Memory (4 times each)	ANAM/MATB Working Memory (2 times each) PVT/FIT	RTSW/Vitals/MSLT PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS
1500	ANAM	RTSW/Vitals/MSLT	RTSW/Vitals/MSLT

	MATB Working Memory (4 times each)	PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS	PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS
1800	ANAM MATB Working Memory (2 times each)	*RTSW/Vitals/MSLT* *PVT/FIT* *ANAM/MATB* *Working Memory* *PVT* *VAS/POMS*	RTSW/Vitals/MSLT PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS
2100		*RTSW/Vitals/MSLT* *PVT/FIT* *ANAM/MATB* *Working Memory* *PVT* *VAS/POMS*	Release
2300 2355	Lights out	Drug dose	

Test Period Two

Time of Day	Day 1 – Training	Day 2 – Training/*Baseline*	Day 3 – Testing
0000			RTSW/Vitals/MSLT PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS
0300			RTSW/Vitals/MSLT PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS
0600 0700		Wake-up	RTSW/Vitals/MSLT PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS
0900		RTSW/ Vitals/MSLT PVT/FIT ANAM/MATB Working Memory VAS/POMS	RTSW/Vitals/MSLT PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS
1200		RTSW/Vitals/MSLT PVT/FIT ANAM/MATB Working Memory VAS/POMS	RTSW/Vitals/MSLT PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS
1500		RTSW/Vitals/MSLT PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS	RTSW/Vitals/MSLT PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS
1800		*RTSW/Vitals/MSLT* *PVT/FIT* *ANAM/MATB* *Working Memory* *PVT* *VAS/POMS*	RTSW/Vitals/MSLT PVT/FIT ANAM/MATB Working Memory PVT VAS/POMS
2100	Report to Laboratory Electrode Application	*RTSW/Vitals/MSLT* *PVT/FIT* *ANAM/MATB* *Working Memory* *PVT* *VAS/POMS*	Release
2300 2355	Lights out	Drug dose	

Appendix B
Testing Order and Times of Tests

Time of test	Test	Length of test
0000	**RTSW****	**20 minutes**
0020	**Vital Signs**	**5 minutes**
0025	**MSLT****	**20 minutes**
0050	**PVT**	**10 minutes**
0105	**FIT**	**3 minutes**
0110	**Grip Strength**	**3 minutes**
0115	**ANAM**	**15 minutes**
0135	**MATB**	**20 minutes**
0200	**Working Memory**	**10 minutes**
0215	**PVT**	**10 minutes**
0230	**VAS/POMS**	**3 minutes**

**** The procedure of putting these two tests together is an accepted practice, as shown in several studies in which both these tests were used (Sugerman and Walsh, 1989; Hilliker et al., 1992).**

Appendix C
Biographical/Medical History Questionnaire

1. Birthdate: _____ Age: _____ Gender: ***Male/Female***

2. Are you currently under the care of a physician for the treatment of: excessive daytime sleepiness, narcolepsy, insomnia, or any other sleep disorder? ***Yes / No***

3. Do you have any drug allergies? ***Yes / No***
   If so, please list them below.

   _____

   _____

4. Do you have difficulty swallowing pills? ***Yes / No***
5. Are you currently taking any medications? ***Yes / No***
6. Are you lactose intolerant? ***Yes / No***
7. Does your medical history include any of the following:
   - Chest pains? ***Yes / No***
   - Heart attack? ***Yes / No***
   - High blood pressure or hypertension? ***Yes / No***
   - General cardiac concerns? ***Yes / No***
   - Kidney disease? ***Yes / No***
   - Liver disease? ***Yes / No***
   - Arthritis? ***Yes / No***
   - Recurrent or chronic pain? ***Yes / No***
   - Frequent headaches? ***Yes / No***
   - Depression? ***Yes / No***
   - Emotional or mental illness? ***Yes / No***
   - Drug abuse? ***Yes / No***
   - Chronic stress? ***Yes / No***

8. Are you currently taking medications for any of the conditions listed above? ***Yes / No***
   If yes, please list them here:

   _____

9. Are you currently taking or have taken within the last 60 days any of the following medications?
   - Aspirin? ***Yes / No***
   - Ibuprofen (Motrin, Advil, Nuprin, etc.)? ***Yes / No***
   - Naproxen (Aleve)? ***Yes / No***
   - Ketoprofen (Orudis KT)? ***Yes / No***
   - Cortisone or other steroid medication? ***Yes / No***
   - Erythromycin? ***Yes / No***
   - Nifedipine? ***Yes / No***

10. What other prescription, over the counter, herbal, nutritional supplements (to include vitamins) medications have you taken in the last 60 days?

    _____

    _____

    _____

11. Have you ever participated in a research study before? ***Yes/No***

Appendix D
Side Effects Questionnaire

Participant Number: _____ Date: _____ Time: _____

Please circle the appropriate rating to each of the symptoms listed below that you are experiencing at the time you complete this checklist.

1	Trouble Staying Awake	None	Slight	Moderate	Severe
2	Chills	None	Slight	Moderate	Severe
3	Loss of Balance	None	Slight	Moderate	Severe
4	Numbness	None	Slight	Moderate	Severe
5	Tingling	None	Slight	Moderate	Severe
6	Chest Pain	None	Slight	Moderate	Severe
7	Diarrhea	None	Slight	Moderate	Severe
8	Dry Mouth	None	Slight	Moderate	Severe
9	Vivid Dreams	None	Slight	Moderate	Severe
10	Rash	None	Slight	Moderate	Severe
11	Itching	None	Slight	Moderate	Severe
12	Swelling	None	Slight	Moderate	Severe
13	Nervousness	None	Slight	Moderate	Severe
14	Anxiety	None	Slight	Moderate	Severe
15	Stomach Cramps	None	Slight	Moderate	Severe
16	Muscle Cramps	None	Slight	Moderate	Severe
17	Visual Illusions	None	Slight	Moderate	Severe
18	"Drugged" Feeling	None	Slight	Moderate	Severe
19	Light Headed	None	Slight	Moderate	Severe
20	Short of Breath	None	Slight	Moderate	Severe
21	Joint Pain	None	Slight	Moderate	Severe
22	Frequent Urination	None	Slight	Moderate	Severe
23	Difficulty Staying Awake	None	Slight	Moderate	Severe
24	Stiff Joints	None	Slight	Moderate	Severe
25	Difficulty Breathing	None	Slight	Moderate	Severe
26	Excessive Thirst	None	Slight	Moderate	Severe
27	Fever	None	Slight	Moderate	Severe
28	Stiff Neck	None	Slight	Moderate	Severe
29	Nasal Congestion	None	Slight	Moderate	Severe
30	Sore Throat	None	Slight	Moderate	Severe
31	Wheezing	None	Slight	Moderate	Severe
32	Bloody Nose	None	Slight	Moderate	Severe
33	Can't Remember Entire Periods of Time	None	Slight	Moderate	Severe

34	Difficulty Remembering Recent Events	None	Slight	Moderate	Severe
35	Irritability	None	Slight	Moderate	Severe
36	Loss of Coordination	None	Slight	Moderate	Severe
37	Insomnia (Sleeplessness)	None	Slight	Moderate	Severe
38	Abdominal Pain	None	Slight	Moderate	Severe
39	Migraine	None	Slight	Moderate	Severe
40	Back Pain	None	Slight	Moderate	Severe
41	Constipation	None	Slight	Moderate	Severe
42	Increased Cough	None	Slight	Moderate	Severe
43	Ear Pain	None	Slight	Moderate	Severe
44	Irregular Heartbeat	None	Slight	Moderate	Severe
45	Tremor	None	Slight	Moderate	Severe
46	General Discomfort	None	Slight	Moderate	Severe
47	Fatigue	None	Slight	Moderate	Severe
48	Boredom	None	Slight	Moderate	Severe
49	Drowsiness	None	Slight	Moderate	Severe
50	Headache	None	Slight	Moderate	Severe
51	Eye Strain	None	Slight	Moderate	Severe
52	Difficulty Focusing	None	Slight	Moderate	Severe
53	Salivation Increased	None	Slight	Moderate	Severe
54	Salivation Decreased	None	Slight	Moderate	Severe
55	Sweating	None	Slight	Moderate	Severe
56	Nausea	None	Slight	Moderate	Severe
57	Difficulty Concentrating	None	Slight	Moderate	Severe
58	Mental Depression	None	Slight	Moderate	Severe
59	"Fullness of the Head"	None	Slight	Moderate	Severe
60	Blurred Vision	None	Slight	Moderate	Severe
61	Dizziness with Eyes Open	None	Slight	Moderate	Severe
62	Dizziness with Eyes Closed	None	Slight	Moderate	Severe
63	* Vertigo	None	Slight	Moderate	Severe
64	** Visual Flashbacks	None	Slight	Moderate	Severe
65	Faintness	None	Slight	Moderate	Severe
66	Aware of Breathing	None	Slight	Moderate	Severe
67	*** Stomach Awareness	None	Slight	Moderate	Severe
68	Loss of Appetite	None	Slight	Moderate	Severe
69	Increased Appetite	None	Slight	Moderate	Severe
70	Desire to Move Bowels	None	Slight	Moderate	Severe
71	Confusion	None	Slight	Moderate	Severe
72	Burping	None	Slight	Moderate	Severe
73	Vomiting	None	Slight	Moderate	Severe
74	Rapid Heart Beats	None	Slight	Moderate	Severe

75	Hand/limb tremors	None	Slight	Moderate	Severe
76	Intoxication	None	Slight	Moderate	Severe
77	Panic	None	Slight	Moderate	Severe

* Vertigo is experienced as loss of orientation with respect to vertical upright.
**Visual illusion of movement or false sensations of movement, when not in the simulator, car, or aircraft.
***Stomach awareness is usually used to indicate a feeling of discomfort which is just short of nausea.

If you are experiencing a symptom not listed above please use the space provided below to describe the symptom(s).

	Symptom Name				
1		None	Slight	Moderate	Severe
2		None	Slight	Moderate	Severe
3		None	Slight	Moderate	Severe
4		None	Slight	Moderate	Severe
5		None	Slight	Moderate	Severe

For each symptom marked YES, do you think the drug caused the symptom?

Symptom Number	YES	NO	If NO, what is the likely cause?

To what extent would the symptom(s) marked YES prevent you from performing normal day-to-day activities?

Impairment	Symptom No.	Symptom No.	Symptom No.	Symptom No.	Symptom No.
Severe					
Moderate					
Slight					
None					

If you knew you would have to stay awake and work for a long period without sleep, do you think you would take the drug to help maintain your alertness in spite of the symptoms you experienced? ***Yes / No***

Place an "X" next to the treatment you think you were given:

- Dextroamphetamine: _____
- Modafinil: _____
- Caffeine: _____
- Placebo: _____

Appendix E
INFORMED CONSENT DOCUMENT

TITLE OF STUDY

The Relative Efficacy of Single Operational Doses of Caffeine, Dextroamphetamine, and Modafinil on Measures of Sleepiness and Performance in Sleep-Deprived Volunteers

Principal Investigator: John A. Caldwell, Ph.D., AFRL/HEPM, DSN: 240-8251, Brooks City-Base TX 78235, *john.caldwell@brooks.af.mil*

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Associate Investigator: Randall W. Engle, Ph.D., Georgia Institute of Technology, (404) 894-8036, Atlanta, GA 30303-3083, *randall.engle@psych.gatech.edu*

Medical Monitor: Carol S. Ramsey, Col, USAF, MC, CFS, Chief of Aerospace Medicine, DSN: 240-8092, AFRL/HEP, Brooks City-Base TX 78235-5100, carol.ramsey@brooks.af.mil

Purpose: You have volunteered to be one of **twenty** participants in the research investigation entitled "The Relative Efficacy of Single Operational Doses of Caffeine, Dextroamphetamine, and Modafinil on Measures of Sleepiness and Performance in Sleep-Deprived Volunteers." The purpose of the study is to evaluate the effects of various alertness-enhancing medications (dextroamphetamine, modafinil, and caffeine) on your ability to remain alert and perform a variety of tests over a 40-hour period without sleep. If one or all of these medications meet expectations, it may be possible to enhance operational capability and safety during long-haul flights and high work tempos. The data will also be used to model the sleep and cognitive performance effects of the three medications to enhance a mathematical model that relates sleep and cognitive performance. Dextroamphetamine is a prescription stimulant that has been available in the United States since the 1950's. It is approved by the Food and Drug Administration (FDA) and is commonly used, at the 10-mg dose, for individuals experiencing narcolepsy (a sleep disorder in which people are excessively sleepy during the day). The United States Air Force has approved dextroamphetamine for use with aircrews attempting to fly long sorties (over 20 hours). Modafinil is an alertness-enhancing drug that is somewhat similar to dextroamphetamine. It was approved by the FDA for the treatment of narcolepsy in December of 1998, and there is great interest in establishing the safety and effectiveness of modafinil for use in military contexts. Caffeine is a common over-the-counter stimulant that occurs naturally in a variety of foods and drinks such as chocolate candy, soft drinks, tea, and coffee. It is estimated that caffeine has been used for hundreds of years to improve alertness in a variety of situations. All three of these medications (dextroamphetamine, modafinil, and caffeine) are considered safe and effective when used by healthy young adults under the type of medical supervision that is present in this research study.

Procedures: This study requires 205 hours of your time **over a period of 12 days**. This time requirement includes: a 12-hour orientation and training day, a sleep period inside the laboratory **at Brooks City Base**, and a 38-hour experimental period **over 4 phases of 3 consecutive days and 2 nights each (each having a drug or placebo during each phase)**. During this study, you should abstain from drug and alcohol use for 48 hours prior to reporting to the laboratory on each of the 4 ocassions, and you will not be permitted to use drugs, alcohol, or caffeine (other than the study dose) during participation. Prior to admission into the study, your medical status will be evaluated by an Air Force physician to ensure that you are cleared to participate. This evaluation will include a screening for current significant medical problems (including sleep abnormalities), current use of medications (other than oral contraceptives, sodium naproxen, ibuprofen, acetaminophen, aspirin, or other medication that will not alter your mental functioning), difficulty swallowing food substances and/or pills, use of nicotine, or excessive use of caffeine (people who normally consume more than three 8-ounce cups caffeinated coffee or five 12-ounce caffeinated soft drinks per day cannot be allowed).

Once accepted into the study, you will undergo several test sessions. During these "experimental sessions" you will be required to perform several simple computerized tests, mood questionnaires, and tests of sleepiness/alertness. These tests will be presented about once every three hours throughout the experimental sessions (except for one short test that will be given approximately every hour). You will receive a dose of medication (either dextroamphetamine, modafinil, caffeine, or placebo) around midnight during the second night of your participation in each of four separate 3-day test episodes. One time you will get a dose of an inactive placebo (a "dummy" pill) and at the other times, you will be given 10 mg of dextroamphetamine, 200 mg of modafinil, and 300 mg of caffeine (during separate test episodes). Even though the amount of mg of modafinil and caffeine are more than the amount of mg of dextroamphetamine, research suggests that these doses should produce roughly the same effects. However, you will not know which of the four compounds you will receive in each dose period because all of them will look identical. Following each dose, you will be asked to perform the tests throughout the night and until about 2100 the following evening. You will not be allowed to sleep during this period, and you will not be allowed to be by yourself (except during "bathroom breaks") so that we can make sure you stay awake the entire time. If you should fall asleep, you will immediately be awakened so that the tests can continue.

Questionnaires: Demographic information will be acquired from you. Other questionnaires will ask you how you are feeling several times during your participation. One of these tests, the Profile of Mood States, will present you with 65 adjectives, and your task will be to record how well each of those adjectives describe your feelings at each test time. The other test, the Visual Analogue Scale, will present you with eight adjectives underneath a series of 100 mm lines, and you will be asked to show how each of these adjectives describes your current feelings by placing a mark along each of the lines.

Alertness/sleepiness tests: Approximately every 3 hours, there will be two objective tests of how alert or sleepy you are. Both of these tests involve the collection of data about your brain activity, eye movements, and muscle activity. This information will be recorded through the use of sensors which will be glued to your scalp, the skin next to your eyes, and the skin under your chin (a standard sleep/EEG hookup). All of this will be monitored by study personnel while you are completing the sleepiness/alertness tests. Both tests will require you to lie in bed in a darkened room, but one test will ask you to stay awake as long as possible (for up to 20 minutes), while the other test will ask you to go to sleep as FAST™ as you can. In both of these evaluations, you will be awakened immediately after you fall asleep.

Performance Assessment: Through your stay in the laboratory, you will perform several series of tests: A 15-minute block of cognitive performance tests from the Automated Neuropsychological Assessment Metrics (ANAM) task will require you to complete math, reasoning, reaction time, spatial, and memory tests on a computer. A 10-minute working memory task called the Automated Operation Span (AOSPAN) test will require you to perform simple math tasks while memorizing a series of letters. A 20-minute "divided attention" task (the Multi Attribute Task Battery) will require you to track a "target" using a joystick while monitoring lights and dials, listening for radio calls and adjusting radio frequencies, and monitoring the levels of fuel in simulated fuel tanks. A brief (30-sec) grip strength test will involve your squeezing a hand-held device as hard as you can three times in a row. A 5-minute fitness for duty test will require you to visually "track" flashing/moving lights presented to you by a special machine. A simple 10-minute Psychomotor Vigilance Task (PVT) will require you to rapidly press a button on a hand-held testing device as soon as numbers appear in a small visual display. This last test, the PVT, will be administered approximately every hour, whereas the other tests will be less frequent.

Polysomnography – On the first night of every 3-day testing episode, you will sleep in the laboratory, and your sleep quality will be assessed. Brain electrical signals (EEG) will be acquired from sensors that are glued to your scalp, eye (EOG) signals will be recorded from sensors attached to the skin near your eyes, and muscle (EMG) signals will be collected from sensors attached under your chin. All of the data collected by these sensors will be used to score your sleep quality.

Discomfort and risks: You understand that there are the following risks, discomfort and/or inconveniences that may reasonably be expected from participation in this study:

Risks: The investigation includes no conditions that will likely lead to disability or death. No pregnant females will be admitted into the study since it is not recommended that this medication be taken while pregnant (this is why, if you are female, you have been subjected to a urine pregnancy test). You are expected to practice effective contraceptive practices throughout this study as a urine pregnancy test generally does not detect a pregnancy until 4-7 days after conception. There are some risks associated with participation in this study, but past work with modafinil, dextroamphetamine, caffeine, and sleep deprivation indicates that these risks are small and unlikely to present problems for you. Nonetheless, you should be aware that the manufacturer of modafinil lists several possible adverse reactions that have been associated with this medication. Across a wide dosage range, occasional

nervousness/excitation, insomnia, sleep disturbance, headache, feelings of elation, and anxiety have been noted; and in doses of over 1000 mg per day, increased heart rate and blood pressure (which were not clinically significant) have been observed particularly in elderly volunteers. There also is a slight possibility of allergic reactions. With dextroamphetamine, the manufacturer advises that possible adverse reactions include: heart palpitations (perceiving your heart beat), rapid heart beats, and increased blood pressure; over-stimulation, restlessness, dizziness, insomnia (inability to sleep), euphoria (feeling "high"), dysphoria (feeling "depressed"), tremor (shaking hands), headache, and, rarely, psychotic episodes (seeing things that are not in fact there); dryness of the mouth, diarrhea, constipation, and/or other gastrointestinal disturbances; loss of appetite with temporary weight loss; and/or changes in sex drive (while taking the drug). The ingestion of excessive caffeine (beyond what you will be given in this study) has been associated with several adverse reactions constituting a syndrome termed "caffeine intoxication". The symptoms include restlessness, nervousness, excitement, insomnia, flushed face, diuresis (need to urinate), gastrointestinal disturbance (stomach cramps), muscle twitching, rambling flow of thought and speech, rapid heart beats, feelings of inexhaustibility, and/or agitation. You are unlikely to experience the majority of these effects, but you should be aware that any or all of them could occur. Besides these warnings about modafinil, dextroamphetamine, and caffeine, you should be aware that prolonged sleep deprivation (beyond what you will experience here) has produced psychotic symptoms in some individuals. However, more typical responses are sleepiness, depressed mood, and impaired mental concentration. If you should experience significant problems with any adverse reactions, you should notify any member of the research staff, at which point a psychologist and a physician will be consulted to take immediate corrective action if warranted.

Due to the amount of sleep deprivation you will experience, it is highly recommended that you allow two full nights of sleep following each test period before you engage in activities such as driving, operating complex machinery, or other potentially dangerious tasks.

Finally, there is a chance that your participation in this study could cause you to "test positive" on some types of workplace drug tests. This is because one of the drugs being evaluated in this study has been known to be a "drug of abuse" in certain populations. This danger of testing positive may persist for as long as 3 days following your release from the study. If you should encounter any problems with a workplace drug test, please notify the pricipal investigator, the medical monitor, or any other study personnel, and indicate to them the name, address, and phone number of your immediate supervisor. We will formally notify them regarding your participation in this research project, and advise them that your positive drug test resulted from the single dose of dextroamphetamine you consumed during the study.

Alternatives: Your alternative is to choose not to participate in this study.

Additional costs: None

Benefits:
a. No direct benefit to you exists for participating in this protocol.
b. Your participation in this experiment will benefit Air Force operational research.

Compensation: You understand that you will bear no costs for medical testing. You will receive from Veridian Engineering, approximately three times the Federal Minimum Wage (FMW is currently $5.15 per hour), or a total of $3075.00 ($15.00/hr).

Privacy Issues
Records of your participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5 U.S.C. 552a, and its implementing regulations. You have read the Privacy Act Statement contained in DD Form 2005. Disqualifying conditions in military members must be reported to the appropriate medical representatives.

Entitlements and confidentiality
Records of your participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5 U.S.C. 552a, and its implementing regulations. You have read the Privacy Act Statement contained in DD Form 2005. Understand that records of this study may be inspected by the U.S. Food and Drug Administration (FDA), the sponsoring agency and/or their designee, if applicable. You understand that entitlement to medical and dental care and/or compensation in the event of injury is governed by federal laws and regulations. If you have questions about your rights or if you believe you have received a research-related injury, you may contact the Brooks City-Base Clinic (311MDS/SGP), Flight Medicine, at 210-536-4987. The USAF will, within limits of

the care offered at the Clinic, provide emergency medical care for any injury sustained as a participant in this research activity. In the event that the USAF emergency care is not available, alternative emergency care will be sought for medical treatment.

If an unanticipated event occurs during participation in the study, you will be informed. If you are not competent at the time to understand the nature of the event, such information will be brought to the attention of your next of kin.

The data which you contribute in this study will be kept as confidential as possible; however, complete confidentiality cannot be promised because information bearing on your health may be required to be reported to appropriate medical or command authorities. Also, representatives of the U.S. Air Force Research Laboratory may inspect the records of this research study. Your individual records will be stored in a locked office which has limited access to individuals not involved in this study. While your name will remain associated with your data, only people directly involved with this study will have access to the information.

Your actual performance data will be stored electronically and will not include any identifying information other than your participant number. Data from the entire group of 20 participants will be summarized in final report documents and will also be used to model the sleep and cognitive performance effects of the three medications to enhance a mathematical model that relates sleep and cognitive performance. Aspects of individual performance may be reported as well, however, your name will never be published as a contributor of specific data points or as a participant in the investigation.

Your decision to participate in this study is completely voluntary. No one has coerced or intimidated you into participating in this program. You understand that if you refuse to participate, you will not lose any benefits that you are entitled to. You are participating because you want to. John Caldwell (AFRL/HEPM/ 210.536.8251) or his representative has adequately answered any and all questions you have about this study, your participation, and the procedures involved. You understand that an investigator will be available to answer any questions concerning procedures throughout this study. You understand that if significant new findings develop during the course of this study that may relate to your decision to continue participation, you will be informed. You further understand that you may withdraw this consent at any time and discontinue further participation in this study without prejudice to your rights. Dr. Ramsey (210-536-8092) (USAF, MC, CFS) the medical monitor, or Dr. Caldwell, the principal investigator, may terminate your participation in this study at any time if he/she feels this to be in your best interest. You have been provided a copy of this consent form.

_____
Participant's printed name

_____ _____
Participant's signature Date

_____
Advising investigator's printed name

_____ _____
Advising investigator's signature Date

I witnessed the participant's signature to this informed consent document.

_____
Witness' printed name

_____ _____
Witness' signature Date

Appendix F
Recruitment Notices

Notice 1

The U.S. Air Force Research Laboratory (AFRL) is conducting a study in which people will be required to stay wake for approximately 38 continuous hours in order to simulate a long mission. Four scenarios will be tested. In one scenario, the alertness-enhancing compound modafinil will be administered to compensate for the difficulty in staying awake throughout the last 21 hours of the wakefulness period. In the second scenario, the stimulant dextroamphetamine will be administered; in the third scenario, caffeine will be administered, and in the fourth scenario, an inactive "dummy" pill will be used. Comparisons among these conditions will help in determining which countermeasure will be useful in safely keeping warfighters alert and therefore, improving alertness and performance. The study will require four periods of three days per period. You will be payed for the amount of time you spend in the research. If you are interested in this study, please contact Laura Sanchez at 536.3615 or go to www.ntiinc.com and link to "Studies".

Notice 2

Sleep research participants

The Chronobiology and Sleep Laboratory at Brooks needs volunteers to participate in a number of ongoing sleep research studies.

Air Force and civilian personnel who are interested and meet the necessary qualifications will receive compensation starting at $15 per hour.

Please contact Laura Sanchez at 536.3615 or go to www.ntiinc.com and link to "Studies".

Appendix G
Information Brief on the AFRL Stimulant Study

The U.S. Air Force Research Laboratory (AFRL) is conducting a study in which participants will be required to stay wake for approximately 38 continuous hours in order to simulate a long mission. Four scenarios will be tested. In one scenario, the alertness-enhancing medicine modafinil will be administered to compensate for the difficulty in staying awake throughout the last 21 hours of the wakefulness period. In the second scenario, the stimulant dextroamphetamine will be administered; in the third scenario, caffeine will be administered, and in the fourth scenario, an inactive "dummy" pill will be used. Comparisons among these conditions will help in determining which countermeasure will be useful in safely keeping warfighters alert and therefore, improving alertness and performance.

Volunteers in this study will be in the laboratory for four periods of three consecutive days each. During the 3-day period, participants will live inside Circadian and Sleep Laboratory (CASL) with meals and sleeping quarters provided by AFRL. Participants will be asked to begin reducing caffeine consumption 2-3 days prior to each test period so that they will be decaffeinated before coming to the lab. (they will not be able to consume caffeine during participation).

The medications to be tested have been proven helpful for keeping people awake and are considered very safe. AFRL is studying the effects of modafinil, dextroamphetamine, and caffeine to determine how well these medications will improve alertness during a long mission, as well as to compare their effects on performance. This investigation will determine how we can benefit performance when personnel need assistance staying alert for long periods of time. Up until this point in time, there have been no controlled, side-by-side, scientific comparisons of these three medications. The results of this testing may provide the military and scientific communities with very effective tools for enhancing the safety and effectiveness of personnel in situations when they must perform their duties when adequate rest may not be possible due to the mission.

Volunteers in this study will be tested for a total of 12 days (1 training day, 1 baseline testing day, and 1 sleep-deprivation day over 4 testing periods). Volunteers will receive the active drug on three of the testing periods, and the placebo (inactive pill) on one of the testing periods. During testing, brain activity will be evaluated using sensors temporarily attached to the scalp; cognitive performance will be measured with computerized tests; and psychological mood will be evaluated using questionnaires. Throughout testing, participants will be expected to follow a specific schedule of sleep and wake-up times, and a certain schedule of testing times.

Please contact Laura Sanchez at 536.3615 or go to www.ntiinc.com and link to "Studies".

Summary abstract

The Relative Efficacy of Single Operational Doses of Caffeine, Dextroamphetamine, and Modafinil on Measures of Sleepiness and Performance in Sleep-Deprived Volunteers

1. **Objectives:**
   - Determine whether measures of working memory capacity, which have been shown to be important in predicting higher order cognition, are sensitive to the effects of sleep deprivation.
   - Establish whether data obtained from working-memory tests will predict differential individual vulnerability to sleep loss (thus indicating that such tests ultimately might be useful for selecting fatigue-resistant individuals for staffing sustained operations).
   - Demonstrate the relative efficacy of single, operationally-oriented doses of caffeine (300 mg), modafinil (200 mg), and dextroamphetamine (10 mg) for sustaining the alertness, mood, and cognitive performance of sleep deprived volunteers.
   - Evaluate the side-effects profile of each of the alertness-enhancing compounds when administered to sleep-deprived participants.
   - Establish the extent to which each compound differentially affects a standardized measure of alertness (the Repeated Test of Sustained Wakefulness) versus a standardized measure of sleepiness (the Multiple Sleep Latency Test).
   - Provide sleep and cognitive performance data upon which to model the effects of the three medications.

2. **Intent:** Conduct a direct comparison among the potential stimulants which may be used by pilots or other personnel during continuous and sustained military operations.

3. **Relevance.** Enhanced operational capability and safety during operations characterized by limited sleep opportunities in combination with high work demands.

4. **Principal Expected Outcome:** Guidance to flight surgeons and commander with regard to determining which alertness-enhancing compound is most effective for particular types of operations. Incorporation of drug effects parameters into the FAST™™ software for use by flight surgeons.

Appendix 2 – AF FAST™ Users
A Listing of AF FAST™ Users and Those Receiving FAST™ from the AF

	Date Sent	Version	Phone #	Organization or Company	Location
1			275-9535	412 TW/ENV	Edwards AFB
3			240-4465	USAFSAM/FEP	2601 Louis Bauer Dr. Brooks-City
7		1.0.23	dsn: 858-0651		89 AMDS/SGPT 1045 Boston Rd. Andrews AFB Md, 20762-5451
9		1.0.26	674-9554	Maj.	AFRL/HEP 837 2729 Rst. Wright-Patterson, 45433-5702
12				US ARMY	
14		1.0.26	dsn 785-0457	maj	
16		1.0.26	757-764-7827	Capt	1 AMDS/SGPT 76 Holly Street Langley AFB, VA 23665
17			527-3710	AFFTC/FM	Edwards AFB
20		1.0.26		capt	97 MDOS/SGOAF 301 N. first st., Bldg 46 Altus AFB, OK 73521
21		1.0.23	dsn: 445-7522	Maj.	166 AW/SE 2600 Spruance Dr. New Castle, De 19720-1615
24		1.0.26		Dr. Psychology	Department of Psych. Weber State University Ogden, UT 84408-1202
25				AFRL/HEPG	
26		1.0.26	314-479-2377	435 AMDS	435 AMDS, Ramstein AB, GE
32		1.0.26		Lt	354 FW/SET, 354 Broadway Suite 13A, Eielson AFB, AK 99702
33		1.0.26	682-2967	Capt	6513 Kenya Springs St. North LV, NV 89081
35				Maj 311 Human Systems Wing	
37		1.0.26	317-626-1881	TSgt	Stop #15 5005 raspberry road anchorage, ak 99502
46		1.0.26	3AMDS/SGPFT	Capt	5955 Zeamer Ave Elmendorf AFB, AK 99506
49				56TRS/APE	
50		1.0.23			910th AW YARS 3976 King Graves rd. Unit 42 CES Vienna, Ohio 44473-5942
51		?	540-761-1576	IN ANG, 181 Medical Group	
54					6255 Sycamore Hill, Indianapolis, IN 46220
55		1.0.26	346-1278	TSgt	
57			527-2305	AFFTC/DS	Edwards AFB
59		1.0.26	246-0880	Maj	9700 G Avenue SE, Kirtland AFB, NM 87117
62		1.0.26		71 MDG/SGOT	Vance AFB, OK 73705
63		1.0.23		LtCol	102 E. Hill Blvd, Suite A, Charleston AFB, SC 29404-5004.

65		1.0.23		60th AMDS, Maj.	
66	14/6/2005	1.0.23		ssgt	60 AMDS/SGPFT 101 Bodin Cir. Travis AFB, CA 94535-1800
67			????	AFFTC/XP	??????
69		1.0.23		437 AW/SEO	
70			527-1407	95 ABW/CEV	Edwards AFB
71			525-9469	AFFTC/JT	Edwards AFB
72	12/7/2004	1.0.23			19301 McGregor Street Beale AFB, CA 95903
73				9AF/SE	Ste 109, 216 Sweeney Blvd, Langley AFB, VA 23665
74		1.0.13		435 AMDS/SGPF	
75		1.0.23			PSC 1 Box 3989 APO, AE 09009
80	15/6/2005	1.0.13		ACC/DRX	
81		1.0.26	574-2417	ACC	216 Sweeney Blvd Suite 104 Langley, AFB, VA 24665
83				514 anw/se	
84		1.0.23		Maj. BSC/PSPTS training	
85		1.0.26	554-4608	capt	215 Base View Dr. S.A. TX 78227
89			525-9534	412 TW/ENV	
93				AFRL/HEPG	
95		1.0.13		TITAN	
98		1.0.26	dsn: 474-6101	Col	
100		1.0.26	228-2969	1st	aerospace physiologist 355 AMDS/SGPF Davis-Monthan AFB, AZ 85707
103		1.0.26	525-3372	Capt.	95 AMDS/SGPT 55 N. Wolfe Ave. Edwards AFB, CA 93524
106	(907) 552-6738	1.0.23		2dLt	
107		1.0.13		HQ AIA/DO2	
Note: Where only a name or Email address was posted to the database, the entire line was omitted.					